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Original Articles

THE TREATMENT OF ACUTE ASTHMA*

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PERHAPS you have not yet suspected it, but physicians commonly will tell the difficult asthmatic patient, "You must go to Arizona." Unfortunately, the physician also may make broad implications that such a trip will prove to be a panacea for asthma. This regrettable situation makes it imperative that Arizona physicians have clearly in mind an adequate program for the management of acute asthma.

Physicians hold many divergent opinions as to the proper long-range management of asthma. These remarks, therefore, will be limited to the treatment of the acutely ill asthmatic patient, a field in which less difference of opinion exists and in which immediate information is of great importance.

Bronchodilating Drugs

The first objective in the management of asthma is symptomatic relief of the acute asthmatic attack. Therefore, the use of bronchodilating drugs is an early therapeutic consideration. The most effective of these drugs is epinephrine hydrochloride. This drug is best given in an aqueous 1:1000 solution. It should be administered early and in adequate amounts to afford prompt symptomatic relief. Usually, the dose ranges from 0.25 to 0.5 ml. as a single injection, or 0.25 ml. can be given at intervals as brief as 20 minutes for the patient seriously ill with asthma. Timid, delayed and inadequate use of epinephrine probably has been the basis for more disastrous results in the treatment of asthma than has its excessive use. Epinephrine should be given, of course, in smaller amounts when such are effective and in those patients having the relative contraindications of old age, vascular disease and hypertension. The early administration of epinephrine prevents an attack of asthma from becoming advanced, with more extensive medication becoming necessary for its control. It is usually preferable to inject epinephrine in an aqueous solution rather than in forms designed for delayed absorption; while the latter vehicles prolong the effect of this drug, they also delay its absorption at times when it may be urgently needed.

In selected asthmatic patients, my colleagues and I have thought it desirable to provide instruction in the self-administration of epinephrine. Patients who are able to do this are much less anxious concerning an attack of asthma than are patients who must depend on the availability of the services of a physician, nurse or spouse for an injection to provide symptomatic relief.

Bronchodilators are also available in the form of nebulized epinephrine hydrochloride or close-

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ly related derivatives of epinephrine, such as isoproterenol. The latter substance has fewer cardiovascular side effects than has epinephrine, while retaining and enhancing its asthma-relieving properties. Epinephrine hydrochloride and isoproterenol given by nebulization afford more prompt relief for the acute asthmatic attack than do ingested medicaments. Also, the use of a nebulized drug is easier than is the administration of those requiring injection. Isoproterenol is likewise available in the form of a powder for insufflation into the bronchial tree, and it can be given in a less effective tablet form for sublingual use. The effect of epinephrine and of isoproterenol by nebulization is usually prompt but transitory. The subcutaneous or intravenous injection of isoproterenol is likely to be associated with excessive cardiovascular symptoms, making it less useful by this means of administration.

An important group of bronchodilating drugs is that of ephedrine and similar drugs. These induce an epinephrine-like effect extending for four to six hours. Indeed, the effectiveness of ephedrine likely exists because of its capacity to slow the rate of enzymatic destruction of endogenous epinephrine. My colleagues and I usually administer ephedrine sulfate in a dose of ⅜ of a grain given orally at four-hour intervals. Unfortunately, many patients react adversely to ephedrine by the development of cerebral excitation or cardiovascular symptoms, which makes the use of the drug of less value. Also, elderly men who have urinary obstruction from prostatic disease may experience acute urinary retention following the use of ephedrine. When such adverse symptoms arise, one may consider the use of ephredine-like drugs, such as methoxyphenamine (orthoxine) hydrochloride or phenylpropanolamine (propadrine) hydrochloride. The effect of these agents, however, appears to be somewhat less than is that of ephedrine.

The xanthine derivatives are an extremely important group of bronchodilating drugs. Of these, aminophylline is the most efficacious. It is most efficient when administered intravenously, being much less effective when given either orally or by rectal administration. For the seriously ill asthmatic patient, we commonly administer 250 mg. of the drug in each liter of those intravenous fluids used initially to hydrate the patient. For a critically ill patient, a more concentrated solution of aminophylline at times may be injected intravenously in order to achieve an immediate bronchodilating effect. However, if the contents of a 10-ml. ampule (250 mg.) of aminophylline are injected directly into a vein or into the tube of a freely running venoclysis set, this should be done very slowly in order to avert cardiovascular effects. For the patient having mild nocturnal attacks of asthma, either suppositories or small retention enemas containing 500 mg. of aminophylline may offer effective anti-asthmatic therapy. However, rectal or perianal irritation develops in some patients from aminophylline used in this manner. In such cases of local distress, suppositories containing other medicaments, such as theophylline methyl glucamine (glucophylline), may be tried.

Hydration

The problem of hydrating seriously ill asthmatic patients is of considerable importance. These patients have eaten poorly, have been drinking less liquid than usual and have perspired freely. They ordinarily enter the hospital in a state of dehydration. On admission to the hospital, such patients usually should be given fluids intravenously. We often administer two to three liters of fluids during the first day in the hospital, the main portion being given in the form of a 5 per cent solution of dextrose in water. The matter of adding sodium to these fluids must be judged in the light of steroid administration and of the possibility of actual or potential adrenal disease. The dextrose provides nourishment and also replenishes glycogen, which has been depleted from the liver by repeated injections of epinephrine. We continue with the intravenous administration of fluids, giving one to two liters daily until hydration is achieved, as evidenced by an increasing urinary output and thinning of the inspissated bronchial secretions. If extensive hydration is required, it is best to be certain that no electrolytic imbalance occurs; this is especially true when steroid therapy is being used simultaneously. In addition to the intravenous use of fluids, we encourage patients to drink generous amounts of water, trying to achieve an objective of a glass of water each waking hour until hydration has been effected. As the state of hydration improves, the intravenous use of fluids can be decreased and then discontinued.

A word of caution is in order concerning those patients in whom the question of potential or

actual congestive heart failure exists. Such patients should be hydrated less enthusiastically and observed carefully for any evidences of pulmonary edema.

Expectorants

One of the most frequently omitted drugs in the therapeutic regimen for the asthmatic patient is an appropriate expectorant to thin the bronchial secretions. It should be noted that the value of an expectorant is limited until hydration has been effected. With hydration and thinning of the bronchial secretions, the irritative coughing may be reduced, thereby greatly enhancing healing of the inflamed bronchial mucosa.

To my knowledge, the most effective expectorant is potassium iodide. One should administer this drug as long as bronchial secretions are tenacious and difficult to raise. Iodides generally are the bulwark of medication used by the asthmatic patient. These usually are tolerated better after meals and when liberally diluted with water. If digestive distress proves troublesome, the use of enteric-coated tablets of potassium iodide may afford some respite. Unfortunately, an intolerance to iodides develops in some patients, with swelling of the salivary glands or an acnelike eruption that necessitates use of less effective expectorants, such as ammonium chloride, as a substitute.

Detergent solutions given by nebulization occasionally are used to aid in thinning and raising the bronchial secretions. While such solutions are occasionally helpful, their use is of limited value because they are in themselves irritating.

Sedation

Asthmatic patients often are emotionally disturbed and usually are profoundly exhausted. Therefore, the judicious use of sedatives is often helpful in bringing relief to the acutely ill asthmatic patient.

As one selects a sedative for use in the asthmatic patient, it is important to avoid drugs that depress the respiratory center. Also, it should be remembered that asthmatic patients often tolerate sedatives poorly. For example, asthmatic patients frequently are stimulated rather than sedated by barbiturates. Those sedatives which are more useful include chloral hydrate and such ataractics as meprobamate, chlorpromazine or promazine.

The practice of giving opiates to the asthmatic patient is to be condemned. These drugs depress the respiratory center at a time when it is already burdened with the severe stress of asthma, and their use is too often a prelude to respiratory failure. At no time should morphine, codeine, meperidine (demerol), dihydromorphinone (dilaudid) or similar opiates be given to a patient in the primary treatment of asthma. During the postoperative care of asthmatic patients, one may use demerol for the relief of pain, because this drug suppresses the respiratory center less than do other opiates. Antihistaminic agents are relatively less important in the management of asthma, although they are at times helpful for their sedative effect.

Cortisone-like Drugs and Corticotropin

The introduction of cortisone-like drugs and corticotropin has given the physician powerful weapons in the management of asthma. While these drugs are useful, their administration should be governed by a rigid framework of qualifying circumstances. These agents are but one facet in the management of the seriously ill asthmatic patient. While their administration usually will bring about rapid and effective control of asthma, such control unfortunately lasts only while the drugs are being employed and for a brief subsequent period. Asthma then will recur unless other measures to control its causes and complications have been successful. The average duration of benefit to the asthmatic patient after the use of such drugs is discontinued is about three weeks; indeed, half the patients are having trouble after one week.

The principal disadvantage of the cortisone-like drugs is that they suppress the activity of the adrenal cortex. This is the consequence of suppression of the anterior pituitary gland, which then fails to elaborate a hormone to stimulate the adrenal cortex. Inasmuch as asthma is a disease often associated with periodic severe stress, and inasmuch as the intact anterior pituitary-adrenal cortical mechanism is a device to splint the body in the event of stress, it is evident that atrophy of the adrenal cortex is a serious problem for the asthmatic patient. Of course, the usual relative contraindications to steroid therapy are as valid in asthmatics as they are in nonasthmatic patients. These include such conditions as peptic ulcers, pyogenic infections, emotional illnesses and tuberculosis. It is important, therefore, that a patient's physical condition be adequately studied and that the indications be clear before steroid hormones are

employed in the management of asthma.

Definite indications exist for the use of cortisone-like drugs in asthma. These include first the critically ill patient who is in such a desperate state that there is insufficient time to assess the influence of more conservative remedies on his asthma. Next, one may use these hormones for those seriously ill patients who are failing to respond satisfactorily to other measures. A third indication concerns that asthmatic patient undergoing severe stress who has, in preceding weeks, received steroid drugs and whom we might consider as potentially having adrenal cortical insufficiency. In such instances, treatment is, at least in part, a crutch to bolster flagging adrenal cortical function. One occasionally encounters a patient in whom great urgency exists in the necessity to bring asthma under control, such as in the pre-operative preparation of a patient suspected of having a malignant tumor; under such circumstances, one may employ steroid drugs, realizing that their use must be continued through the major stress of the operative procedures to follow. There are certain surgical procedures in which the control of cough and asthma is especially important, as in the repair of large postoperative ventral hernias; one might consider the use of steroid drugs as being indicated for such conditions.

With respect to the program of steroid medication, my colleagues and I prefer the use of periodic, discrete courses in the management of asthma. These courses usually extend less than three weeks. The latter days of a course are utilized in decreasing the dose of the steroid being administered. We do not consider that steroids should be used in place of other more conservative types of treatment, but rather as a supplement to other forms of therapy. When longer courses are used, one often encounters great difficulty in discontinuing the use of steroid drugs. In general, the longer the period of therapy, the more prolonged should be the process of tapering off as administration of the drugs is discontinued. If these agents have been used for months or years, several weeks are necessary for the gradual reduction in doses, perhaps with decrements no greater than 10 per cent weekly, before their use ultimately is discontinued. In our experience, the use of periodic courses of corticotropin (ACTH) with the hope these will stimulate the patient's own adrenal function has proved of little value as an adjunct in discontinuing a prolonged course of steroid therapy. Whereas problems with electrolytic disturbances were once a significant part of treatment with cortisone, we find these to be less frequent with shorter courses of the more recently available steroid drugs.

Specific Steroid Drugs

My colleagues and I infrequently use cortisone in the management of asthma. Its interest is primarily historical. The only occasion for which we still employ it is the preparation of a surgical patient who has received large amounts of steroid drugs. We then give intramuscular injections of slowly absorbed cortisone to splint the patient through the ensuing period of operative stress.

Hydrocortisone also is used much less frequently than it was formerly, although we still employ it primarily because of its solubility, which enables one to administer the drug intravenously and thereby start quickly a program of steroid therapy.

Prednisone and prednisolone can be considered together because of the similarity in their use. Prednisolone is perhaps slightly more potent than is prednisone, yet the doses generally employed in implementing therapy are similar. We usually give these medicaments orally at six-hour intervals in divided doses. The initial dose is 10 mg. every six hours. This dose is gradually halved over perhaps three days as a therapeutic response is being achieved. Toward the end of such a course of treatment, the dose is tapered off and then use is discontinued.

More recently, we have given triamcinolone or methyl prednisolone in a similar course of therapy; however, the doses are 80 per cent of those employed with prednisolone or prednisone. The latter drugs actually may not only be free of a tendency to cause retention of sodium, but actually may bring about a slight loss of sodium.

A still more potent steroid drug now is available in the form of dexamethasone. A dose of 0.75 mg. of this agent is the equivalent of 4 mg. of methyl prednisolone or triamcinolone, and it is the equivalent of 5 mg. of prednisolone or prednisone.

Our use of corticotropin has decreased in recent years. One reason for this concerns the necessity for its injection. Although the use of gels as a vehicle has reduced the number of in-

jections that are needed, the necessity for injection still persists. Perhaps a more pressing reason is that corticotropin, to be effective, must stimulate an adrenal cortex that is capable of responding. Therefore, if steroid therapy is urgently needed, one is safer in relying on steroids administered directly rather than to rely on their indirect release by corticotropin. When we do employ corticotropin in the treatment of asthma, we use it in the form of a gel, administering doses every 12 hours, usually starting with doses of 40 units and reducing them to 20 units as a therapeutic effect is achieved.

Less effective but still a useful adjunct in steroid therapy is the topical use of nebulized prednisolone. This form of treatment circumvents the systemic effects of steroid drugs and exerts a local effect on the bronchial mucosa. In this technic, one may use a solution containing 10 mg. of prednisolone per milliliter; 2 to 3 ml. of this solution, mixed with a like amount of a 0.5 per cent solution of isoproterenol, is nebulized daily, perhaps in six sessions.

Gas-Inhalation Therapy

The inhalation of gases in the treatment of asthmatic patients is employed less today than it was a decade ago. However, when cyanosis is associated with asthma, the use of oxygen or of a mixture of helium and oxygen still occupies a place in an anti-asthmatic regimen. We prefer the use of oxygen by a BLB mask to its administration by a tent or a nasal catheter. The variable need for oxygen by the patient who has uncomplicated asthma makes the use of a mask more readily adaptable to the particular situation. When oxygen is employed by mask, a volume of six to nine liters per minute usually suffices; this amount should allow the rebreathing bag on a BLB mask to be not quite empty at the height of inspiration. A mixture of 80 per cent helium and 20 per cent oxygen, given either directly from a tank in that proportion or further diluted with equal parts of oxygen, is used by many physicians in the treatment of asthma. The patient receiving helium has a high-pitched, squeaky voice that may alarm him if he has not been forewarned about this.

Particularly to be avoided is the administration of oxygen in generous quantities to patients who have advanced pulmonary emphysema, because such patients may be adversely affected by oxygen therapy. With severe pulmonary emphysema, a certain degree of oxygen want affords an essential continuing stimulus to the flagging respiratory center. If an abundance of oxygen suddenly is made available, respiratory failure and loss of consciousness often develop. When oxygen must be administered to the emphysematous patient, it should be used in restricted quantities, and the patient should be carefully observed for confusion or for evidences of respiratory failure.

Many varying opinions can be found concerning the desirability of positive-pressure breathing devices, such as the Bennett valve and the "Mines Safety Ventilator." Patients generally do not prefer the administration of oxygen by means of positive-pressure mechanisms. The major usefulness of such devices is in patients having an element of pulmonary edema or perhaps when they are used intermittently in patients who have emphysema.

My colleagues and I commonly give carbon dioxide by inhalation for asthmatic patients following upper abdominal operations. Such operations make deep breathing painful and are likely to be followed up by atelectasis. Inhalations of 95 per cent oxygen and 5 per cent carbon dioxide at hourly intervals will stimulate deep breathing and thereby reduce the possibility of atelectasis.

Environmental Control

An important aspect in the management of asthma concerns control of the patient's environment. Hospitalization should be considered for the seriously ill asthmatic patient, especially one who is responding poorly to measures introduced for care in the home. Hospitalization immediately removes the patient from allergens encountered in his home. When time permits, dustproof covers should be applied to the mattress and pillows in the hospital room prior to the patient's arrival. Kapok should not be used as a substitute for feathers because of the frequency with which patients grow allergic to it. Foam-rubber pillows and mattresses are satisfactory for use by most patients. Sweeping should be avoided in the room, as this resuspends dust in the air. Floors should be cleaned with a damp cloth. The better control of humidity and temperature possible within the hospital greatly favors the healing of bronchitis, which all asthmatic patients have to a greater or lesser degree. During seasons when pollens to which a patient may be allergic are in the air, a pollen

filter should be placed in the bedroom window to permit only pollen-free air to enter the room. Doors, transoms and other means by which pollen-laden air might enter a room obviously should be kept closed.

It is desirable to place the acutely ill asthmatic patient in a private room. In a ward, it is difficult to control dust, feathers, cosmetic preparations, various offending respiratory irritants and guests of other patients. Asthmatic patients often have their greatest trouble at night, and this engenders in others an apprehension that is not lost on the asthmatic patient. Hospitalization removes the patient from the constant overt anxiety of solicitous relatives.

Many measures that are necessary in the adequate treatment of asthma are more readily available in the hospital than in the home. This includes the inhalation of therapeutic gases, the parenteral use of fluids and the early administration of injected medicaments. However, if hospitalization is not available, much may be accomplished with modifications of a home routine to adapt the care to the needs of the asthmatic patient.

Objectionable Procedures

Certain procedures should be mentioned as objectionable. As already discussed, the use of opiates should be avoided because of their suppressive effect on the respiratory center. Likewise, one should avoid therapy with burning stramonium powder, which, while affording a measure of temporary relief, aggravates the bronchitis and perpetuates asthma. One should avoid preparations containing arsenic because of the hazards of arsenical intoxication. Asthmatic patients should not smoke, because this aggravates bronchitis. Sedation should be used sparingly. Many remedies used in treating asthma include a small amount of a sedative, and the accumulative effect of many sedative agents should be avoided. Asthmatic patients should not be encouraged to cough hard. Many asthmatic patients believe that bronchial secretions are noxious and must be expectorated. Such patients cough repeatedly and unnecessarily in attempts to raise bronchial secretions. By mechanical irritation, these patients perpetuate the problem of bronchitis. As the secretions become thinner, one should urge patients to suppress excessive coughing. Rest for the inflamed bronchial mucosa is a prerequisite for healing.

Bronchitis

As indicated previously, each patient with asthma has some degree of bronchitis. If a patient has purulent sputum or other evidences of bacterial infection as suggested by fever or by the thoracic roentgenographic findings, the use of antibiotic drugs should be seriously considered. However, administration of antibiotics should be avoided in the absence of a specific indication. Results of cultures of sputum, with determination of the sensitivity of the organisms involved to various antibiotics, should determine the selection of a proper antibiotic agent. In those patients receiving prolonged antibiotic treatment, the sensitivity studies should be repeated occasionally. The flora of the bronchial tree will change following antibiotic therapy in a manner analogous to the changes induced in the flora of the gastrointestinal tract. In addition to the oral and parenteral administration of antibiotic drugs, one may nebulize antibiotics, particularly if infection resolves slowly or if an element of bronchiectasis is present.

With subsidence of the acute phase of asthma, one has much more latitude in evaluating the basic causative factors that have brought about the asthma. An otorhinolaryngologist can determine if chronic disease exists in the paranasal sinuses; if such disease is present, surgical measures for more adequate drainage might be considered. Likewise, one should consider an allergy survey at this time. Such studies should be deferred to this point because the patient's illness necessitates the use of drugs that may interfere with cutaneous reactivity. Emotional factors that have been important should be given more adequate consideration. The question of bronchoscopy might be considered.

Conclusions

The asthmatic patient has an illness that is greater than its allergic aspects alone. These patients often present problems involving many systems. It is unusual for a patient to have asthma in the absence of any other pathologic changes. The use of potent weapons in the management of asthma presupposes an accurate appraisal of the entire patient, not merely his respiratory symptoms and especially not merely the immunologic aspects of these symptoms. Only if the entire patient, his other diseases, his emotional problems, and the ultimate effects of the treatment being given are reviewed can the best care for asthmatic patients be afforded.

GOLD IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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SINCE October 1932, there have been 3,120 patients with a positive diagnosis of rheumatoid arthritis who have been studied and followed for varying periods of time in our practice. Gold salts have been a valuable agent in treatment in this group since 1933, although in the early years it was not used in the mild cases unless response to other treatment was considered inadequate. However, since 1940, it has been given to all patients with reversible rheumatoid arthritis who were in good health otherwise. Individually, the duration of gold therapy varied from one injection to continuous use over a 20-year period and the total amount from 10 mg. to 11,890 mg. administered intramuscularly.

Koch, in 1890, reported the results of his experiments that demonstrated the inhibition of the growth of tubercule bacilli when they were exposed in a gas of gold cyanide. It was one of the harbingers of chemotherapy and, in 1913, Feldt reported the bacteriocidal properties of certain preparations of gold which contained a sulfhydryl group. In 1927, he demonstrated the effectiveness of gold thioglucose against experimentally produced streptococcic and spirochetal infections in mice. The same year, Lande and Pick independently discussed the effect of gold salt therapy in patients with rheumatoid arthritis, and in 1928, Forestier began to use it intensively, reasoning that if gold salts were of value in other chronic diseases, such as tuberculosis, they might be effective in rheumatoid arthritis. The first of his several reports appeared in 1929 and provided the impetus for the use of gold salts generally.

The criteria for the study included a history, complete physical examination, pertinent laboratory data, and x-ray examination. An individual program was explained in detail to each patient. It consisted of weekly intramuscular injections of gold salts, a minimum initial period of three weeks' complete bed rest, physical therapy (including instructions in exercises), psychotherapy, use of analgesics, sedation, and orthopedic aids, and, when indicated, steroid therapy. Those making up the "control" group were given the same over-all instructions, with the single exception that gold salts were not administered. A few patients received small amounts of Streptococcus vaccine in its place.

Only patients who had been observed weekly for a minimum of three months were included in this study. There were records of 507 patients who received gold salts and 566 control patients. It was decided, further, for purposes of evaluation, to divide the gold-treated into groups of those who had received a total of more or less than 300 mg. of gold salts. There were 369 patients who had been given more than this amount and 138 who had received less. This latter group consisted of patients who had manifested sensitivity to gold, who were started on gold therapy recently, or who had discontinued this treatment by their own choice.

The gold salt was given intramuscularly at

TABLE I

Response to Therapy of Patients with Mild, Moderate, and Severe Rheumatoid Arthritis, with Comparison of Group Receiving Minimum of 300 mg. of Gold Salts and Control Group.

	Degree of Rheumatoid Arthritis															
	Mild						Moderate						Severe			
	Gold Treated			Controls			Gold Treated			Controls			Gold Treated			Controls		
Response	No.	Per Cent		No.	Per Cent		No.	Per Cent		No.	Per Cent		No.	Per Cent		No.	Per Cent	
Excellent	8	14	56	6	7	34	19	13	68	10	4	44	4	2	49	4	2	35
Major	23	42		23	27		79	55		93	40		80	47		83	33	
Minor	21	38		47	55		40	28		98	42		69	40		125	55	
None	3	5		9	11		4	3		30	13		19	11		38	15	
Total	55			85			142			231			172			250		

weekly intervals, beginning with a dose of 10 mg., then 20 mg., and then 40 mg. weekly. If no signs of sensitivity appeared, treatment was continued until 500 mg. had been given. At this point, the weekly dosage was determined on the basis of the patient's clinical status. Those with moderate or severe arthritis usually required weekly injections of 40 mg. until 800 mg. had been administered, then 20 mg. for four weeks, 10 mg. weekly for four weeks, 10 mg. at increasing intervals, and finally 10 mg. once every four weeks for years. Those with mild symptoms were not given as much gold salts after the first 500 mg., since the dosage was cut more rapidly to be leveled eventually at 10 mg. monthly for years. It should be stressed that, during the period of dosage of 10 mg. per month, should exacerbation occur, the dose of gold salts given should be increased and the intervals between injections shortened in order to control the symptoms.

The gold was injected into the deltoid muscle, with use of a 24-gauge, ¾ inch needle, which produced no inflammatory reaction, was well tolerated, and was easier to administer than into the gluteal region. At each visit, prior to injection, the patient was questioned concerning signs of sensitivity, especially glossitis or dermatitis. Complete blood-cell count and urinalysis were done every three or four weeks.

Summary

Since October 1932, 3,120 patients with a positive diagnosis of rheumatoid arthritis have been studied. Since 1940, gold salts have been given to all patients with reversible rheumatoid arthritis who were in good health otherwise. The gold salt was given intramuscularly at weekly intervals, the initial dose being 10 mg., then 20 mg., and then 40 mg. weekly. If no signs of sensitivity appeared, treatment was continued until a minimum of 500 mg. had been given. Use of gold salts affords patients 20 per cent better chance of complete recovery or of major improvement. Severe reaction to gold occurs in a very small percentage of patients.

EL ORO EN EL TRATAMIENTO DE LA ARTRITIS REUMATOIDE

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En nuestra práctica, desde octubre de 1932 hemos estudiado y seguido por un período variado de tiempo, 3,210 enfermos con diagnóstico positivo de artritis reumatoide. Desde 1933 las sales de oro han sido un tratamiento de valor en este grupo de enfermos, auque en los primeros años no se usaron en los casos medianos más que cuando no había respuesta a otros tratamientos. Sin embargo, desde 1940 la hemos administrado a todos aquellos enfermos con artritis reumatoide reversible que por otra parte estaban en buenas condiciones de salud.

La duración de la terapia con el oro en cada enfermo, varió desde una inyección hasta una administración sostenida durante 20 años con un total de 10 miligramos a 11,890 miligramos, administrados por vía intramuscular.

Koch en 1890 reportó los resultados de sus experiencias que demostraban la inhibición del crecimiento del bacilo tuberculoso cuando se le exponía a la acción del gas de cianuro de oro. Este experimento fué uno de los pioneros en la quimioterapia. En 1913 Feldt reportó las propiedades bactericidas de ciertas preparaciones de oro que contenían el gropo sulfhidrilo. En 1927 él demostró la efectividad de la tioglucosa de oro contra las infecciones estreptocócicas y por espiroquetas producidas experimentalmente en las ratas. El mismo año, independientemente Lande y Pick discutieron el efecto de las sales de oro en enfermos con artritis reumatoide y en 1928 Forestier empezo su uso sistemático, razonando que si las sales de oro tenían valor en otras enfermedades crónicas, tales como la tuberculosis, probablemente ellas debían de ser útiles en el tratamiento de la artritis reumatoide. Su primer reporte aparecío en 1929 y produjo un gran entusiasmo por el uso de las sales de oro en general.

El criterio para este estudio, además de la historia cl:nica, con exámen físico completo, datos de laboratorio y de Rayos X, implicó un programa individual para cada uno de los enfermos consistente en una inyección intramuscular por semana de sales de oro, un período inicial mínimo de 3 semanas de reposo en cama completo, fisioterapia (incluyendo instrucciones y ejercicios) psicoterapia, uso de analgésicos, sedación, ayudas ortopédicas y, cuando estaba indicado, terapia con esteroides. El grupo control recibió las mismas instrucciones con la única excepción de que no se le administraron sales de oro, en su lugar algunos de ellos recibieron pequeñas cantidades de vacunas estreptocócicas. Sólo fueron incluídos en este estudio los pacientes que observaron por tres meses como mínimo. 507 enfermos recibieron tratamiento y 566 sirvieron de control. El primer grupo se subdividió en un primer subgrupo de 369 enfermos que recibieron más de 300 miligramos de sales de oro y un segundo subgrupo de 138 enfermos que recibió menos de esa cantidad. Este último subgrupo estuvo formado por enfermos que manifestaron cierta sensibilidad al oro, que empezaron su tratamiento recientemente o que por algún motivo descontinuaron su tratamiento.

Taba No. 1.

Enfermos con artritis reumatoide ligera, moderada o severa y su respuesta a la terapia de un mínimo de 300 miligramos de oro. Comparación con un grupo control.

(Véase la tabla en la transcripcion en inglés)

La sal de oro fué administrada por vía intramuscular a intervalos semanarios, empezando con una dósis de 10 miligramos, 20 miligramos y luego 40 miligramos por semana. Cuando se presentaron signos de sensibilidad el tratamiento se continuó hasta que se hubieron administrados 500 miligramos. Entonces, la dósis semanal se terminó en base de las condiciones clínicas del enfermo.

Aquellos con artritis severa moderada recibieron semanalmente inyecciones de 40 miligramos hasta completar 800 miligramos, bajado

luego a 20 miligramos por 4 semanas, entonces a 10 miligramos semanales otras 4 semanas, luego 10 miligramos a intervalos crecientes y por último 10 miligramos cada 4 semanas durante varios años.

Aquellos enfermos con síntomas medianos recibieron pequeñas cantidades de las sales de oro después de completar 500 miligramos por ejemplo 10 miligramos mensuales durante varios años. Debe observarse que si durante el período de la administración de 10 miligramos por mes se presentaba alguna exacervación de la enfermedad la cantidad de sales de oro se aumentaban y se acortaban los intervalos de sus administraciones.

El oro se inyectaba en el músculo deltoides con una aguja número 24 sin producir reacciones inflamatorias; se toleraban bien y fué más fácil de administrarse que en la región glútea, previamente, a cada inyección se investigaba que había habido signos de sensibilidad, especialmente glositis o dermatitis y una cuenta globular hemática y un uriánalisis era hecho cada 3 o 4 semanas.

Sumario:

Desde octubre de 1932, han sido estudiados 3,120 enfermos con diagnóstico postivo de artritis reumatoide. Las sales de oro se administraron desde 1940 a todos los enfermos con artritis reumatoide en buenas condiciones generales, a una dósis semanal de 10, 20 y 40 miligramos progresivamente, por vía intramuscular. Cuando no representaron signos de sensibilidad, el tratamiento se continuó hasta un mínimo de 5-500 miligramos administrados.

Un 20% de los enfermos se recuperó o presentó gran mejoría; sólo un pequeño porcentaje de ellos presentaron reacciones severas a la sales de oro.

BIOLOGICAL AND CHEMICAL WARFARE IN CIVIL DEFENSE*

By Cecil H. Coggins,
Captain (MC) U.S.N.

Introduction of Capt. H. Coggins, MC, U.S.N. by Paul C. Thompkins, Ph.D., scientific director, U. S. Naval Radiological Defense Laboratory, San Francisco, Calif.

THE next speaker is one who needs no introduction to those who have long been concerned with ABC warfare. He has for many years been engaged in the field of mass-casualty producing weapons. A postgraduate of the University of California in nuclear medicine, he was the first officer in the military services to be designated as biological warfare officer, which post he held in the navy.

For three years he served in the office of the chief of naval operations as chief of the ABC warfare section, during which time he represented the United States Navy on international committees and missions. In 1950 he was appointed special assistant to the supreme commander of the allied forces in Europe, for ABC warfare. In this capacity, he organized schools for training in ABC defense in each of the NATO countries. He is consequently well-known in both Europe and America as an authority on this subject, and therefore, without further ado, I will introduce Capt. Cecil H. Coggins.

Gentlemen — During this symposium you have already heard a great deal about the deadly effects of the atomic bomb — and of the fallout following an explosion — and you will hear a great deal more. As military leaders and responsible citizens, you are quite naturally seriously concerned with the tremendous power and unique potentialities which attend atomic explosions.

But this morning I wish to invite your attention to still another effect of the atomic bomb — one that has been generally overlooked, but which, in the course of time, might eventually prove to be the most disastrous effect of all! I am going to call this the "blinding effect," and by that I do not mean the loss of visual purple in the retina, which results in temporary optical blindness. I refer, instead, to the paralyzing effect which the contemplation of atomic war seems to have had on our powers of reasoning. We have become so blinded by the brilliance of nuclear fission that we have well-nigh forgotten all else!

This is clearly evident when we review the books, manuals, charts and other literature devoted to civil defense. In more than a dozen of the most recent books on this subject, including last year's records of the hearings on civil defense before the congress, there are not a half-dozen pages in which weapons, *other than atomic bombs*, are mentioned. Even fire storms are presumed, in these publications, to be caused by atomic explosions — in spite of the fact that the most disastrous storms in history have been those resulting from incendiary bombing. In the future, incidentally, we may expect still more destructive fires to be caused by massive flights of incendiary rockets. The truth is, that while our heads have been in the mushroom clouds (as it were), not only have all of the old, conventional weapons been vastly improved and perfected — but also new and ingenious means of producing mass-casualties have been developed — adopted and emphasized — and this is particularly true on the other side of the Iron Curtain.

In this situation there lies a very great danger. Over the past two years Mr. Andrei Gromyko and Nikita Khrushchev have been beating their drums of propaganda in a persistent public demand for atomic disarmament. The crescendo is now rising with increased insistence upon a summit conference, to that end. The Russian proposals, as usual, have been hedged about with impossible conditions, and consequently, up until now they have fallen upon deaf ears. But it is entirely conceivable that the day may come when the people of the free countries of the world may be frightened or tricked into the abolition of atomic weapons, without at the same time insuring against the employment of other weapon systems. If and when that day

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comes (may God forbid), we shall be in great difficulty and in great peril. You are already well aware that under those circumstances the enemy will have a tremendous superiority in manpower.

I think I can show you that he will also be ready and willing to attack the free world, using the weapons of mass destruction remaining to him, namely the biological, chemical and possibly, radioactive substances.

The Chemical Threat

Let's first consider the chemical threat. On his state of readiness at this moment, I can say very little. I do know, however, as long as five years ago he had 106 chemical plants in operation, at least of which one half were devoted to war gases. His stocks then of the newest German war gases greatly exceeded the combined stocks of the free nations, being quite sufficient for three, or four major offensives on a wide front. At the same time the equipment, training, indoctrination in gas discipline of his troops far excelled that of our own and those of our allies. There was even a curious and I think, very significant difference between the Russian warfare training manuals and our own.

The Russian texts referred to the war gases in that direct confident matter of fact tone that one would use for an old and familiar weapon, while our own publications generally, and have for many years, treated the use of gas as though it were a theoretical and probably remote contingency, yet one which the well-educated soldier ought to learn about.

I must here hasten to say that more recently, under the fine leadership of the present head of the chemical corps, Gen. William Creasy, our chemical warfare manuals have been very greatly improved, but it is shocking to note that some responsible military and civil defense leaders still seem to regard chemical warfare as having only theoretical or historical significance. In my experience, these individuals are invariably those who have had neither training nor experience in chemical warfare and their attitude moreover, reflects precious little familiarity with military history.

In order to gain an idea of the potentialities of the modern gases one has only to read of the gas attacks of World War I, where the most Force, and for one-tenth of all the casualties of primitive gases and the crudest generators, used only a few times, accounted for one-third of all the casualties of the American Expeditionary the entire World War, and yet the gases of today are at least 15 times more deadly than the old, and moreover, they are now distributed by a dozen different superior modern means, including rockets, guided missiles, airplanes, mines, explosive projectiles and land generators, all of which have been field tested and proved to be workable and efficient. It has been found a simple matter to build up a concentration of gas which will blanket large areas and bring death to all not provided with gas masks.

It is not true that launching a gas attack involves a risky gamble with the weather. Not only can weather conditions be predicted with accuracy, but also diurnal fluctuations bring favorable conditions which will insure the success of an attack. Mobile munitions have made wind direction no longer a factor. The cold, stark truth is that modern war gases have become tremendously effective weapons. From the military point of view, they are absolutely superb in their ability to wipe out whole populations of cities and to do so after having been delivered on target from long distances by means which have already been perfected. As civil defense leaders, you must realize that they will not only be the principle weapons of a non-atomic war, but also important auxiliary weapons even when atomic bombs are used. As, for example, when an enemy desires to preserve such an area intact for his own purposes.

The certainty that modern war gases will be used against your civil defense derives from four unassailable facts. First, that the gases are very effective and efficient weapons. Second, that the enemy possesses them in great quantities. Third, that he has the knowledge and means to use them and fourth, that he will not hesitate to do so whenever it will be to his advantage.

Now, you may say that last is a conclusion rather than a fact, but if it is, it is certainly a very valid conclusion, because it rests upon overwhelming evidence from world-wide sources that the Communists have always been, and still are, unscrupulous opportunists. For this reason, we must conclude that the Russian will use gas whenever it suits his purpose. Any other conclusion would be reckless and perhaps suicidal, and once we have come to such a conclusion, common sense and prudence demands that we

act upon it.

What is our present state of readiness in civil defense to meet a gas attack?

Suppose we were attacked today, right here in San Francisco, with our military and civil defenses exactly as they are now. What would be the result? Would you like to know? If so, I will do my best to give you an accurate idea.

What It Would Be Like

It is really no longer terribly difficult to *predict* the effects of a gas attack on a typical American city, thanks to Col. John Wood of the medical department of the army. Colonel Wood, working under the secretary of defense, made an exhaustive analysis of the many factors which influence the movement and concentration of a gas cloud in a modern city. The wind variations and the humidity and temperature effects. The hot surfaces and pavements and the resulting turbulences, the windows, whether open or shut, or shattered by high explosives. The population either busy at their tasks, or evacuated, or already on the run. All these variable factors of time, place and circumstance which influence the final result, and then he reduced these findings to a few simple, understandable tables which now serve as guides in studying gas attacks on cities.

Now, we know just what the effect will be, when for example, one square mile of a city is covered to a height of 10 meters by a cloud of nerve gas with an average concentration of 50 milligrams per cubic meter. We know from these studies that the center of the cloud will drift three miles within 30 minutes with a wind speed of six miles per hour. We know that the cloud will double in height and width for each mile of travel for the first 20 minutes while covering two miles, but after that it will hold its height and width unchanged while covering the third mile. By that time 98 per cent of the gas potential has been expended by dilution, but the cloud will already have covered 11.5 square miles and in the average American city will have affected 172,000 people.

The next question is, just how will it have affected them? Thanks to Colonel Wood, and to many field trials, special studies, careful calculations, and hundreds of experiments, we now know this answer fairly well. We also have the experience which has been gained by a good many hundred industrial accidents with nerve gas so that we know what effect a given percentage of nerve gas has on the human being.

Again I want to emphasize that these figures are as accurate as they can be made, and therefore we must regard them as reliable and conservative estimates.

Here we see that the population has been divided into six categories which now have become almost classical. The formula of 20, 30, 15, 15, 13, 16 might almost be used to mean *"Gas Attack on City."* We see that the first 20 per cent get off scot-free. Why? Heaven only knows. Perhaps they were on the wrong level, or in shower baths. Perhaps they were in work-in ice-boxes. They might even have been in shelters, but we do know that this first 20 per cent belongs to that well known and statistically recognizable fraction of lucky individuals who fall downstairs and out of high windows without injury, who wander unscathed through the most violent earthquakes and even the thickest fringe of the gas cloud, but certainly they are on the fringe of becoming casualties. They have been exposed to a concentration of 0 to 7 mgs. of nerve gas per cubic meter. They may have headaches, mild eye pain or a slight tightening of the chest, but these symptoms are regarded as harassing only, and these people could take care of the more serious cases *if* they don't panic. The next 15 per cent are known as the mild cases. They breathe a concentration of 7 to 15 mgs. per cubic meter. They have a frontal headache, dim vision, chest constriction and a runny nose, but they can move about. They don't really have to have atropine, but remember, they have no way of knowing that they're not seriously poisoned. Consequently, they may easily panic. The next 15 per cent are in real trouble. They have been breathing a concentration of nerve gas of 15 to 40 mgs. per cubic meter, and while they're called moderate cases, they need atropine, without which, a certain proportion of them are going to die. They have throbbing headaches, beginning respiratory distress. They are restless, tense, drooling and anxious. Some have twitching muscles and show evidence of confusion. The next group are the 13 per cent who have inhaled nerve gas in a concentration of 40 to 100 millimeters. Their condition is serious. Their poisoning is severe. They show nausea, ataxia, apathy, depression and recurrent painful abdominal cramps. If they are to live they must have repeated doses of

atropine, plus artificial respiration when cyanosis and respiratory failure become evident. The last group, 16 per cent have had it. They breathed an atmosphere containing 100 to 200 mgs. per cubic meter of nerve gas. They show rapidly progressive symptoms of coma, Cheyne-Stokes respiration, violent convulsion with incontinence and central depression of respiration occur, paroxysmal spasms of the tongue and throat. These victims are doomed.

Hypothetical Attack

All right you say, you have divided the victims of a gas attack into categories. What about a gas attack on San Francisco?

Very well, let's set the conditions. First, the weather will be typical of San Francisco with stable temperature gradient, neutral or inversion, the wind six to 15 miles per hour, the humidity 75 per cent, all average mind you, not optimum conditions. The time is 1000 on Friday, June 20. The enemy has approached within 500 miles of the coast before showing up on our radar screens. In less than an hour from now his bombs will begin to drop on the streets of San Francisco. What our defensive forces are going to be able to do in this hour, I'm not going to guess. I hope better than at Pearl. Ten heavy bombers loaded with nerve gas are headed for San Francisco. Each carries 10 tons of bombs; a total of 100 tons.

Although no less an authority than the chief of the U. S. Air Force has testified before the congress that 70 per cent of such an attacking force may be expected to get through our defenses, which would be in this case, 7 planes, I am nevertheless assuming that *only one bomber* will be able to pass over the city! Furthermore (I am an incurable optimist), I am assuming that only one-half of his bombs are dropped with accuracy into the city, and since in these five tons a full half are casing and hardware there remains only 2½ tons of nerve gas which is actually liberated into the city of San Francisco and even then, it appears that these bombs failed to touch a single military or industrial target of any importance.

Instead, these bombs splatter down in a ragged line from the corner of Golden Gate Park, across the San Francisco College for Women and Presidio Avenue, and thence to Broadway. There is a minimal loss of life and property from the explosions, and there is almost no residual gas, most of the nerve gas having been completely vaporized. At first glance it would seem that we have been lucky, but let's have a little closer look to examine the results. It's evident right away that these 2½ tons have been dropped in an area of one square mile and there has been produced consequently, an average of nearly 60 mgs. per cubic meter. Let's superimpose our known pattern of dispersion in the direction of the prevailing breeze to find out just where our 11.5 square miles of gas victims will be.

Now, this picture is staggering. First of all, our map shows that three-quarters of a million people are in the northeast corner of this city, with a half million in one postal district. That is the area between Broadway and Market streets, which includes Chinatown and the financial district. Now, it is apparent that our loss of life is going to be frightful. How many people are in this gassed area? The overlay shows that in this area of 11.5 square miles there are actually 582,000 persons. To see what will become of them let's return to our formula of 20, 20, 15, 15, 13, 16. First, we see in the gassed area, but escaping injury are 116,000 persons. How they react to the sight of the dead and dying around them is largely a matter of training. The great difficulty will be that all of the conditions for panic are present. That is, a danger *which is unknown, which is silent and which is invisible.* The frightening appearance of the victims, struggling for breath and in violent convulsions, the sounds of groans and screams arising from a hundred city blocks, and most of all, the feeling of imminent destruction in an environment where there is a rapidly narrowing or limited escape route to safety. Panic will occur at elevators, staircases, fire escapes and even in the streets. The passage of cars and trucks is blocked, which they will be, by thousands of bodies of persons dead and dying. Now, such panic as this quickly becomes widespread, and the loss of life occuring in the precipitous struggle to escape, very often, has exceeded that due to the primary cause of the panic. Now, the first 116,000 have escaped injury from the nerve gas cloud, but how many hundreds of them are going to die on the staircases of the office buildings?

Let's pass to Category Two. Here is another group who are just as subject to panic as the first group is, and even more so, because they

do have some symptoms, which to them, can only seem exaggerated in an environment of catastrophe. How many of them will destroy each other in a fight to escape? How many will hurl themselves from open windows? How many will be stunned, apathetic and unresponsive, or how many will find the strength to resume purposeful activity for the benefit of their fellows? I can predict the physical casualties with reasonable certainty, but the psychological damage is beyond my power to predict. What of the 15 per cent who are mildly poisoned? The same is true for them. As for the others, they really don't have to have atropine, but their symptoms are frightening. They don't know how great their danger is, and neither does anyone else, and it is *probable* in this group that panic will occur! Their beginning dimness of vision is in itself a terrifying symptom which will contribute to the urgency of their sense to flee. These 87,000 people cannot be expected to render much help to others, even if they have been trained.

This completes the first three classes of those who were injured. They total more than 300,000 and they're scattered over 1,100 city blocks. They hold in their own hands the power of survival or of extinction, both for themselves and for the thousands of real gas victims.

Let's turn now to these. Here are some 87,000 persons moderately gassed, but they need atropine. Some of them more than one dose. They're gasping for breath, clutching their middle and fighting to get into the street. Another 75,000 are still more seriously ill. They're vomiting, or staggering, or lying on the ground in violent convulsions. They each must have several doses of atropine if they're going to live. Many will require prolonged artificial respiration, some of them even tracheal intubation for recovery.

The final group of 93,000, which to external appearances is indistinguishable from the last category, are nevertheless beyond hope. They will simply die a bit more quickly and their bodies will be found in the streets, the stairways and the offices.

What is the overall picture three hours after the attack? We can only conjecture, but it appears exceedingly unlikely that help will arrive in time to save the seriously gassed. The streets are choked with the bodies of the ill and with those already dead. For this reason the passage of ambulances and relief vehicles through the streets is impossible, but more than that, it is quite pointless, since more patients will be encountered in the first few blocks than the entire hospital system can care for.

Communication systems are paralyzed. Only busy signals are heard on the automatic phones. Approximately 350,000 atrophine syrettes are needed. The pitiful few syrettes that arrive are quickly used on the periphery of the stricken area. At the end of six hours (that is four o'clock in the afternoon), there are 120,000 dead and 60,000 dying and 80,000 crying for medical care. Not until the next day, the morning of June 21, will medical aid even begin to reach into the gas area, and more than a week will elapse before all of the bodies are removed. It is probable that panic will be found to have claimed several thousands, and consequently, that the final death toll will be 225,000.

Now, in order to produce such casualties by atomic weapons, the enemy would use at least a bomb of 40 kilotons in energy; that is to say, twice the bombs that were used at Nagasaki and Hiroshima.

This is, I think, ladies and gentlemen, a fair and conservative picture of an attack with modern chemical weapons. Frightful? Yes, it is. Alarming? I certainly hope you'll find it so. Unavoidable? Unpreventable? Certainly not. On the contrary, with a reasonable amount of training, an adequate supply of atropine, and a relatively inexpensive modification of our modern ventilating systems, 95 per cent of this loss of life can be avoided. There's even a small inexpensive device which will *prevent it altogether!*

This device is a gas mask. "Oh," but you say, "Can the American public be persuaded to carry gas masks?" Perhaps not right now, but it can be done with effort and inspiring leadership. Britain did it; of course the time was war. Eighty per cent of the British still have their gas masks. The citizens of Great Britain, Denmark, Sweden, and Russia all have some protection today; pretty good. The U. S. almost none. Britain is preparing even now to distribute new masks to every citizen, free of charge. Here we only have a few masks in the war surplus stores, and for sale by the mine safety people, for industrial purposes. The country with the best gas discipline is Russia. This isn't surprising when we know positively that Russia is prepared to use gas in any war which comes. Not only do we know this, but the Com-

munist leaders are no longer trying to conceal their intentions. Their minister of war has already announced his intention of using biological warfare and chemical warfare. Under this circumstance, one cannot help but wonder what more is necessary to convince our American citizen that the price of liberty is the ability to meet all weapons of mass destruction.

Biological Warfare

While you're pondering over this affair, let's pass on to biological warfare. Here again we have a weapon, or a weapons system, capable of producing mass casualties which has been known for centuries, but which has undergone extensive research and remarkable development in the past 15 years.

The important thing now is just where does BW, or biological warfare stand in the military arsenal of war? Where does it stand today? You'll not find a full and convincing answer to this question among the distressingly meager publications of the civil defense agencies. In more than 136 publications which have been offered for training purposes in civil defense, not more than five or six deal with the subject of biological warfare by more than a casual reference. Some of these are: a pamphlet called *What the Farmer Should Know About Biological Warfare,* another one called *What You Should Know About Biological Warfare,* Training Bulletin 1118 called *Biological Warfare Against Public Water Supplies,* Technical Manual 11-10 of 1953 entitled *Defense Against Biological Warfare,* and, in addition, the "Bible," 24 pages representing exactly 10 per cent of the Handbook AG-11 called *Health Services in Special Weapons Defense* published in 1950.

The second of these, *What You Should Know About Biological Warfare,* was written by someone who apparently was determined that the public never know any more than he knew about biological warfare, which was to say, precisely nothing. In pleasing contrast, however, to this, the other manuals are well and carefully done. They suffer only from the serious handicap of being restricted to unclassified information. Incidentally, while it may be unavoidable, I believe that this handicap is the most important inherent weakness in civil defense education. In order to stimulate their interest and enlist their whole-hearted co-operation, the general public needs to be told more than is presently regarded as fit for their ears! Now here, the military services enjoy a great advantage in being able to provide their personnel with the wide variety of classified information on a *need to know* basis. As we might expect within the services, large numbers of papers, staff studies and reports, and military manuals, have been written which deal fully with the threat of all three ABC weapons, and they provide increasingly realistic guidance for defense against them. Do these military publications answer our questions about the importance of biological warfare? Yes, they do. What is the answer? Well, bearing in mind the fact that this talk is unclassified, I'll nevertheless try to give you a satisfactory answer within that limitation. If some details seem to be conspiciously lacking, please bear with me. First of all, you must know that enormous strides have been made in biological warfare since World War II, and even since the last civil defense publication on the subject. Here in the U. S., our policy has been one of defense. Our research is primarily to perfect defenses against biological warfare attacks, but we found out long ago that defense and offense are inseparable research problems. One cannot be tested without the use of the other. I have no figures on this matter, and if I did, I wouldn't feel free to use them, but I will make a guess that approximately 33,000 scientists' years and nearly one-half billion dollars has been spent on biological warfare research problems. As a result of this tremendous research program, even unclassified publications of the military services will now frankly acknowledge the probable effectiveness of biological warfare agents.

For example, the Bureau of Medicine and Surgery syllabus states, "Agents of biological warfare may be selected to produce many strategic, and certain tactical goals, ranging from a brief, but crippling disease, to widespread serious illness with many deaths." Again, as a result of our research with biological warfare defense, the U. S. Joint Chiefs of Staff placed biological warfare in the highest strategic category, on a level with atomic warfare, and publicly declared their intention to maintain a state of readiness which would enable the American forces to retaliate in overwhelming fashion with biological warfare attack, when and if biological warfare weapons are ever used against us.

Can anything be said which is more convincing than that? I should state that all the

progress in biological research has not been made by the U. S. Many of our allies have joined in studies to insure that we have effective defense, and some of the finest work has been done by them. Just what has been accomplished? Well, I can assure you that while the biological warfare experts have as yet no Hiroshima or Nagasaki to point to as proof of the pudding, nevertheless their activities have not been confined to ivory tower guessing or windy extrapolations of laboratory data. It is known that hundreds of field trials have been held and that sometimes live and virulent agents have been tested and scores of munitions perfected. Attacks have been simulated against entire cities the size of San Francisco, and after careful calculation, large casualties declared by the referees.

Time after time, live, but, harmless agents, have been used in simulated sabotage operations against important strategic and tactical forces of the military population, with results sometimes staggering in their implications. Trial attacks have been made on a great variety of both crops and animals with results that should convince the most skeptical admiral, general, or civil defense leader.

Is all this known to the Russians? If it isn't, then it's because they can't read English. We know for example that the Russians have always had a great interest in Camp Detrick, Maryland. We know that over the past 15 years they have collected hundreds of books, magazines, and newspaper articles which have been so conveniently published for them in the U. S. Not only about Camp Detrick, but about the laboratories at Edgewood and Dugway, Utah, and the Naval Biological Laboratory right here in Oakland. We also have definite information that the Russians have carefully followed the work being done within these laboratories by the simple expedient of collecting all our scientific journals and collecting from them the scores (I should say *hundreds*) of articles relating to biological warfare research which have been published regularly in them by the *very same scientists* who are doing the work! Now, I don't doubt that such research work has, by being published, contributed heavily to the sum of human knowledge and the welfare of man, as well as to the professional reputations of the authors, but I declare without any doubt of hesitation that it has also contributed very heavily to the enemy's state of readiness to use these dangerous weapons against our own U. S.

What else do we know? We know that in addition to scavenging the work done in other countries, which includes Japan, Germany, China, Poland, and in others, the Russians have done independent work of their own on plague, anthrax, botulinus toxin and the salmonella group. We know furthermore, than their own research work has been hastened; hastened as it was in the field of guided missiles, by the importation and utilization of many German biologists and technicians. What do we know of the enemy's real intention regarding biological weapons? So far as I know, we only have one important clue, and this was provided five years ago when the Russian government suddenly and blatantly accused the U. S. before the whole world of having launched biological warfare offensive in Korea. Acting on the sound psychological principle that no lie succeeds like a big lie, and with the expertness born of years of constant practice, the Communist leaders concocted a whole series of brazen fabrications and propped them up with dozens of brain-washed and well coached eye witnesses. Having launched their charges over the radio, news services, and even before the United Nations assembly, these bold prevaricators tied up the whole bundle of propaganda in the form of a book solemnly entitled *America's Guilt in Biological Warfare*, and they put a copy of it in every library in Europe and Asia which would accept it. Why? There is only one explanation that makes sense and that is that the Russians were trying to document a fake incident; trying to give historical weight to their false charges so that, perhaps years from now, they might say, "History shows that it was the U. S. which, in 1952, first used biological warfare on a large scale. The attack which we launched last week was only in retaliation!"

Where and How?

Now, the $64 question is this: If the Russians do attack with biological weapons, where and how will they attack, with what organisms and with what result? This is a question I have very often been asked, and it's probably the most difficult question which could be asked in the whole realm of ABC warfare, not only because it presupposes an intimate knowledge of Russian intentions, which I haven't got, and capabilities, which could do credit to any intelligence

organization in the world, but also an honest straightforward answer should be supported by factual data, the kind of data which is usually non-existent, or else buried under a heavy layer of security restrictions.

Now, please don't misunderstand me. I think such restrictions are properly necessary. I approve of them. I'd have more of them rather than less. There is nothing, however, to prevent us from describing briefly a purely hypothetical biological warfare attack on one of our cities, and there is no practice more useful than this in the training of our defensive forces. Let us suppose, then, that a state of increased national tension in which our own forces have been on a continous alert for the past two weeks exists. Our radar warning net is fully manned. Submarine and surface patrols are being manned right now at sea, and a large corps of coast watchers are patroling the beaches. At 2000 on the evening of Oct. 1, there is a light westerly breeze of five knots which pushes a thick blanket of fog from the ocean across the beach and up the hill of the Richmond district and Golden Gate Park of San Francisco. The humidity is 85 per cent, the temperature 65 degrees, and the temperature gradient stable, and a condition of inversion prevails.

Three miles off the beach, completely hidden by fog, a snorkel breaks the surface, is quickly joined by a periscope and an object that looks like a steel flower on a stem pipe. The three objects, less than a yard apart, proceed in a leisurely, northward direction. The periscope slowly rotating and seeing nothing but fog. Suddenly, the steel flower bursts into a white cloud of vapor as the nozzles are turned on. The vapor mixes with the fog silently and drifts shoreward. After holding a course parallel with the shore for 20 minutes during which time she has traveled two miles, the submarine dives and disappears from the surface.

In this 20 minutes, 200 gallons of a rich bacterial culture has been sprayed from the nozzles. Ninety-five per cent of the particles are less than five microns in diameter, 50 per cent of them are less than one micron. One hundred gallons of this culture is a mixture of pasturella pestis, the organism which causes plague, in a concentration of six times 10 to the ninth per milliliter, and the other 100 gallons is a culture of bacterium tularensi in a concentration of 7.8 times 10 to the ninth per milliliter. These two slurries are physically, chemically and biologically compatible. The organisms have been treated to improve their viability and power to travel, and both are cultures from highly virulent strains.

The fog lifts, or is dissipated, before it reaches 19th Avenue, but the invisible cloud of organisms continues eastward. By 10 p.m., it has reached Divisidero Street. Forty-five minutes later it is spread across the Embarcadero and is reaching across toward Alameda. On the way across the city, the aerosol is subject to a thousand eddys, crosscurrents and turbulences. It flows through open windows and under doors to become a secondary aerosol within thousands of homes. It will persist there for hours and days. It is strongly sucked into the ventilators of factories, office buildings and theaters, to be circulated again and again through a hundred thousand pairs of lungs. The cloud of germs passes across the bay, turns southward, and is finally dissipated 25 miles from its starting point. Nothing more occurs which could give a clue to the fact that an attack has occured. Nothing is happening, except within the bodies of the victims, who still don't know that they are casualties in a war. The hands of the clock turn around through 48 hours and a strange thing happens. Everybody in the family begins to cough, slightly at first, and then with increasing violence. Chest pains appear, temperatures start to rise. Strangest of all, the doctor's phone is busy. Apparently he has left it off the hook. Now, another doctor cannot be reached! Finally, *all* the doctors' phones appear to be busy! Here begins the panic, even before the symptoms of the disease become fully developed.

Rush to the neighbors to get help? Too late! The neighbors are already in the streets comparing notes with other neighbors. The population turns to the radio and to their TV sets. Anxiety mounts at first, as the first disconnected, puzzled and incomplete news is released. The public is urged to be calm. This exhortation has just the opposite effect. The third night comes and goes. In the morning, there are few left standing erect and well. Now, the radio states that a disease epidemic has occurred, that doctors are flying in from a dozen cities, that antibiotics are on the way, that all persons are ordered to stay off the streets and await the arrival of relief trucks. A new sound is heard. The screams and cries of panic are

changing to cries of grief. Across the entire northern part of the city, in every home, the breathing of the patients is becoming labored. Cyanosis has developed, coma is supervening.

Before the week is out, there will be 190,000 deaths. The following week 80,000 more. Part of these are primary infections and part secondary. The third week will show a drop to 14,000, as the broad spectrum antibiotics begin to take effect. The fourth week only 2,000, and the back of the epidemic will be broken. Is there need to continue to describe the utter desolation of the people, the grief, the rage, the despair? There is no need to speak of the frantic efforts to identify these diseases and isolate the organisms, which is conducted by a dozen special teams from the National Health Institute, the Hooper Foundation, the University of California, and Stanford. There's no need to mention the panic in the streets, the shooting, the governor's proclamation, the martial law, the arrival of the militia, the pitched battles between the citizens of Walnut Creek, Petaluma, and Richmond, and the fleeing citizens trying to leave the stricken area. No need to tell of the thousands of homes found abandoned and empty, except for the bodies left behind. Why mention the stench, the parade of trucks piled high with corpses, the huge graves dug by steam shovels? No, I'll leave that to your imagination. All I want to say is, that in the end, by our calculations, 286,000 people have died and an equal number have recovered, out of a total exposed population of 1,250,000, of which 825,000 are primary exposures and 420,000 (down in the peninsula), exposed to secondary infection.

The rate of infection is about 46 per cent of the total population, and of the people who have become ill, nearly 50 per cent are dead. This is the sort of result that may be expected when the human being is simultaneously exposed to massive doses of virulent strains of two different pathogenic organisms. If results such as these are possible, and all of our experimental work seems to indicate that they are, then we must concede that biological warefare is as worthy of our attention as atomic warfare.

You can draw your own conclusions. Apparently our enemies have long since done so. I have here a translation of a lecture given 18 months ago by Col. Adam Milkovich of the Russian army. Colonel Milkovich is also a doctor, a bacteriologist, and he is a professor in the Moscow Institute. Colonel Milkovich says (I quote), "In a practical sense, the question of the possibility of the use of biological warfare weapons in future wars is not considered today a subject open to debate, for it is known that an enemy can successfully attack human beings, and even animals and plants, with biological agents," and again in the same lecture he says, "From results of comparative studies of losses of life from conventional weapons, war poisons, and atomic energy on one side, and losses from biological weapons on the other, it is believed today that a biological war would have the greatest effect of all," and finally he said, "Since biological weapons are so regarded today as more dangerous, not only than conventional weapons, but also more dangerous than chemical and atomic ones, we believe that at least the same attention should be given to this question as to chemical and atomic weapons." (I never thought I'd see the day when I agreed with a Communist.)

There is little more than I can say about this subject at this kind of a meeting. I simply want to say, I know many of you have attended ABC training courses, which were given by the military services under various security classifications, so there is much that you already know, more than I have told. For those of you in responsible positions in civil defense organizations, who have not yet attended such courses, I most sincerely urge that you do so at your earliest opportunity. I believe that it is only from such training that sufficient information is obtainable to constitute a solid foundation for realistic thinking. By now, however, you should have heard enough to convince you that biological weapons are real, and that they constitute a serious threat to our safety, in time of war, and that they must be included in any realistic civil defense operation and training.

Realistic Program

What, then, can be regarded as a realistic program of civil defense? Briefly, it is a program which includes provisions to meet the threat not only of atomic bombs and local disasters, but also of other major weapons likely to be used against us.

It includes organization, training, and material. We must provide ourselves, not only with burn kits, but also with atropine syrettes. Not

only with bandages, but also with BAL ointment. Not only with Geiger counters, but also with the disease-warning system. Our ventilation intake filters must not only protect us against fallout particles, but also against bacteria and poison gas. Our decontamination procedures must also provide for biological and chemical, as well as radiological decontamination. Above all, our training program must *remedy,* and not *contribute* to our blind spots; this dangerous preoccupation with things atomic. We live in perilous times and events move very rapidly. The state of our preparedness for defense must be of gravest concern to every citizen.

What can we say about our preparedness? About 50 years after development of the most deadly gas that the world has ever seen, our entire civil population is without respirators of any sort, and even the masks of our military personnel are locked up tighter than were the ammunition boxes at Pearl Harbor. That is even more serious than the lack of personnel dosimeters, a deficiency that will, after an atomic attack, cause half the precious reserve of blood to be poured down the rat-hole of asymptomatic, and yet hopelessly irradiated patients. In this latter case, a great many people will be saved. In the former, there will be no survivors. Perhaps there are many of you who agree that vigorous action is needed to remedy the deficiencies that I've mentioned. Perhaps some of you are thinking, "*They* really ought to do something about this. *They* must give us the needed equipment. The authorities ought to furnish us with the information that we really need," and so on. I have a very strange feeling, and yet it's quite a strong one, that "*they*" are sitting out there in front of me at this very moment! That the real authorities are right here in this room. Since only knowledge can confer real authority, and nearly all of you have special knowledge, training and skills, which you are already devoting to our national defense, I rather think then, if our efforts, our defenses, are to be improved and perfected, it will be through *your* efforts and efforts of similar groups all over the country. *You* have the power, and at the same time, the responsibility, for assuring that our defenses are adequate to meet *any attack* made against them, including that which may be made by biological or chemical weapons! I wish you good luck!

ABSTRACT
PNEUMATOSIS INTESTINORUM HOMINIS*

With A Case Report

The title of this presentation "pneumatosis cystoides intestinorum hominis" will be interchanged often with the following terms: pneumatosis, pneumatosis intestinalis, intestinal pneumatosis, blebs, blisters, vesicles, gas cysts, intestinal gas cyst, intestinal blebs, intestinal vesicles.

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PNEUMATOSIS Cystoides Intestinorum Hominis is presented in an extensive paper in addition to a case report, thus increasing the number of reported authentic cases in the medical literature.

Apart from the general description of the entire problem of pneumatosis intestinalis, a review of the existing literature was made: particular consideration was given to a number of theories and views regarded as very authoritative in explaining the etiology and pathogenesis of this disease.

The case described in the original presentation was diagnosed preoperatively. Most of the reported cases were found during the performance of autopsies and few were accidentally discovered during an operation for intestinal obstruction.

Pneumatosis Cystoides Intestinorum is a rare disease and the first quite orderly description was reported in 1728 during an autopsy by Du Vernoi. Since so long a time, approximately 230 cases were reported in the medical literature.

Until 1956, 49 cases were authenticated in the United States, of which just a few were diagnosed pre-operatively; some were found during surgery, and the rest while performing autopsies.

Pneumatosis Cystoides Intestinalis is frequently observed in a number of animals and with particular frequency in pigs. It is reported to have been reproduced experimentally in hogs and other domestic animals.

Patients afflicted with this disease are extremely emaciated and bed-ridden for a number of years due to its chronic nature. It may be affirmed that pneumatosis seldom if ever appears in an acute episode in the early stage of the disease. Because of the chronicity and slow progress of the malady, and progressive changes of personality, the average patient does not seek medical attention. It is usually the patient's family who become aware of the gradual deterioration of the afflicted, and proper medical attention is then provided; such decision coincides often with the symptoms of an acute intestinal obstruction.

Seemingly slow progressive inanition and the resulting involvment of the gastrointestinal tract, establishes a peculiar apathetic behavior.

The evoked indifference and drastic changes of personality in those who are chronically affected with intestinal pneumatosis is likewise characteristic and of diagnostic importance in paralytic ileus, and intestinal obstruction, not associated with this pathologic entity.

The presented original paper discusses thoroughly the emotional and personality changes resulting from the effects of this disease and the symptomatic characteristics of pneumatosis, in addition to those enumerated in the case report, as observed in vivo.

In referring to medical history, it is revealed that the ancient Hebrews of the Talmudic era of the land of Canaan and Babylonia, can be credited with originating the science of pathology 2,000 years ago, *by their discovery that diseases may be associated with morphological changes in the organs of the body and become manifest by structural alternations and functional abnormalities.*

Structural alterations were the basis of their doctrine. In the main, it conforms with the theories promulgated by modern science.

The anatomic structural and histoligic changes of the organs resulting from diseases were the fundamentals of the Talmudic doctrine. Their great knowledge of anatomic pathology was mainly obtained from the observation of slaughtered animals. They were able to ascertain

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the course and lethal outcome of many diseases on the basis of the existing pathological condition. The main reasons for this historical oblivion of medical progress for a period of 20 centuries, was due to the fact that the then overall existing physicians could not read the Talmud and were not able to understand the Babylonian teachings of that particular time. The Talmud was rather considered as a Corpus Juris of ritual law, rather than a treatise on medicine.

The history of medicine and the progressive knowledge obtained in animal pathology which may even be referred to Pneumatosis Cystoides Intestinorum Hominis and Animalis, reveals that Rudolph Virchow and Julius Cohnheim, 19 centuries later, finally rediscovered pathological anatomy as the basis of our modern teachings.

The great acquaintance of the ancient sages of Babylonia with visceral pathology, obtained from innumerable autopsies made on domestic animals, contributed enormously to the progress of comparative anatomy, experimental surgery and diagnosis.

In reviewing the past and present literature, the impression remains that the incidence of pneumatosis afflicts mostly the middle age group of the male population, followed by females and children.

Cystic pneumatosis was seldom described as a primary affection, due to its unknown pathogenesis and variable syndrome.

The most frequent recorded findings including those in the presented case, are the almost constant association with chronic disturbances along the gastrointestinal tract and its adnexa. The most common pathology encountered is the presence of pyloric stenosis, gastric and duodenal ulcers, chronic appendicular infection, progressive intestinal obstruction. However, any chronic, morbid affection of the alimentary tract, regardless of its location, may predispose to the formation of intestinal gas cysts.

The main characteristic of Pneumatosis Cystoides Intestinorum is the formation of multiple gas cysts of variable size localized primarily under the visceral serosa of the bowel. Particularly susceptible is the intestinum tenue; however, the simultaneous involvement of the large bowel, stomach, duodenum and jejunum is often present.

Apart from the occurrence of gas cysts in the visceral serosa of the intestine, their presence is also noted to a lesser degree in the submucosa and muscularis mucosae. These air bubbles in the deeper layers are visualized in the form of small, flat, wart-like elevations covered by normal appearing mucosa, or they assume a sessile or pedunculated configuration.

The subserosal blebs are transparent and separated from each other by a very fine structure of connective tissue in a honeycomb pattern. The formation of gas cysts often appears in the form of clusters of grape-like configuration. The continuous increase of these gas filled cystic compartments causes enormous crowding and overlapping, which often assumes the aspect of large granulomas; the incidence of intussusception and volvulus is quite frequent, due mainly, to its increased weight and size, by telescoping through the adjacent segments of dilated intestine. The diagnosis made, as expected, is usually of intestinal obstruction; however, regardless of surgical intervention and relief of obstruction, the main pathology is rarely recognized.

Seemingly, in the last decade the increased number of reported cases indicates that the knowledge of the existence of Pneumatosis Cystoides Intestinorum is becoming gradually more known to the medical profession. The available textbooks of pathology and surgery do not mention pneumatosis intestinalis, and this study recommends further acquaintance with this rare pathologic entity.

The clinical picture of a patient afflicted with pneumatosis reveals great loss of weight, distended abdomen, atrophy of subctaneous tissues, and visible intestinal peristalsis through an emaciated abdominal wall. The skin is subicteric and ashy in color. They usually claim to enjoy good appetite and to have an adequate intake, however this does not seem to be true.

Apart from clinical history and complete physical examination, the greatest information may be obtained from roentgenograms.

A gastrointestinal series followed by a motor meal and barium enema in subjects afflicted with pneumatosis reveal typical honeycombed, translucent configurations which are interpreted as the presence of air bubbles retained within the intestinal wall.

It is often found that the process of pneumatosis involves also the mesenterium and omentum.

The presence of a pneumoperitoneum lacking

the typical alarming clinical symptoms of a perforated hollow viscus, should remind us of the possibility of pneumatosis intestinalis.

The pathogenesis and etiology of this rare disease are not clearly understood. At the present time, there are five theories explaining the origin and cause of this intestinal affection. The existing theories are of bacterial, mechanical, chemical, nutritional and neoplastic origin, and are extensively described in the presentation.

THEORY OF LYMPHATIC HYPERTENSION OF THE ALIMENTARY TRACT

The author of this presentation sustains the theory of the existence of lymphatic hypertension affecting the entire alimentary apparatus. The cause and formation of gaseous cysts within the intestinal wall is probably due to the direct effects of osmosis and lymphatic hypertension. The presence of ascitic transudate which accompanies pneumatosis is found to be frothy and of oily consistency, and seems related to the digestive chyle products which may be termed, when present in greater amounts, as chyloperitoneum.

The presence of free air under the diaphragm in pneumatosis intestinalis is probably the result of continuous release of gasses from within the blebs retained under the visceral serosa.

Seemingly the entire lymphatic system of the digestive tract is involved, with particular accentuation of the antimesenteric surface of the intestine, probably due to the increased circulation required by the Peyer's lymphatic aggregates. Polyserositis, or so-called Pick's disease, may follow the same mechanism, and finally present the characteristics due to lymphatic hypertension, regardless of the origin of its etiology.

The presented case of pneumatosis was submitted to an abdominal laparotomy, because of an intestinal obstruction, resulting from an intussusception of a large pneumocystic granuloma. The exploration revealed that the obstruction was in the terminal ileum. A segmental resection was performed with an uneventful recovery.

The patient was seen again three months later because of postprandial nausea followed by vomiting which was reported to have begun two weeks prior to her return visit. Extremely dilated small loops were noted roentgenologically, particularly in the upper right quadrant. Her status deteriorated rapidly with increased vomiting and abdominal distention. Gastric suction was attempted, but the tube could not be advanced beyond the jejunum.

A second laparotomy was done approximately six weeks after rehospitalization, and the roentgen findings confirmed the presence of a jejunoduodenal volvulus, which was easily disengaged. No abnormalities attributable to the first laparotomy were found, and the resected area was completely healed, with complete arrest of the pneumatosis. Despite these apparently favorable factors and the short duration of the surgery, the patient became moribund and died 14 hours later.

Autopsy revealed a grossly distended "hour glass" stomach and small intestine, the latter showing marked discoloration below the ligament of Treitz. The jejunum and its mesentery presented a tortuous, edematous, discolored appearance and the jejunum was filled with gas and fluid. No evidence of gaseous cysts were found. A presumptive diagnosis of a cerebrovascular accident, taking place just before or during surgery, was made.

Summary

1. A review of the world literature of Pneumatosis Cystoides Intestinorum Hominis, with a case report, is presented. It occurs rarely in man and is of unknown pathogenesis.

2. Formation of gaseous cysts on the intestinal visceral serosa and through the intraluminal mucosa occurs along the gastrointestinal tract as a result of this pathologic condition. A foamy, oily transudate is a concomitant finding.

3. The disease is chronic, of unusually long duration and progresses slowly, causing emaciation, invalidism and personality changes. Presenting symptoms are those of chronic progressive intestinal obstruction.

4. Etiological theories are explored. A working hypothesis of lymphatic hypertension is formulated.

5. Segmental resection of intussuscepted terminal ileum resulted in arrest of cyst formation and general improvement of patient.

6. Intervention for strangulated jejunum, three months after resection, was delayed by patient beyond safety.

7. Autopsy showed good results of first laparotomy and revealed jejunal strangulation. A presumptive diagnosis of a cerebrovascular accident, before or during surgery, was made.

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Comentarios y Conclusiones

PNEUMATOSIS CYSTOIDES INTESTINORUM HOMINIS*

Con la presentación de un caso clinico

El título de este trabajo, "pneumatosis cystoides intestinorum hominis" a menudo se intercambiará con los siguientes términos: pneumatosis, pneumatosis intestinalis, intestinales pneumatosis, vejiga, ampolla, quistes de gas, quistes de gas intestinales, ampollas intestinales, vejigas intestinales.

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EL CASO clinico descrito revela que este enfermo fué enviado para operarse en 1953 con el diagnóstico de "Fistula colecisto-duodenal con calculo biliar impactado en la válvula ileo-cecal produciendo oclusión intestinal intermitente." El diagnóstico post-operatorio fué "Vesícula que no functiona, peritonitis generalizada, etiología no determinada." La serie gastroduodenal pre-operatoria mostró pneumoperitoneo. La existencia de pneumatosis como padecimiento no fué reconocida. Las placas simples de abdomen tomadas en el postoperatorio, 10 a 15 dias después, confirmaron la notable disminución en el pneumoperitoneo, pero una pequeña cantidad de aire era visible todavia bajo el diafragma derecho. La disminución en la cantidad de aire fué debida probablemente a la presencia de dos canalizaciones colocadas en los cuadrantes superior e inferior derechos, cuando se hizo el diagnóstico radiológico. En Febrero de 1957, el radiólogo hizo el diagnostico de "padecimiento quístico grave del mesenterio" por primera vez. En Marzo de 1957 se presentó una obstrucción intestinal, y los hallazgos operatorios fueron: "Pneumatosis generalizada del intestino delgado con formación de grandes granulomas incluyendo formaciones císticas con gas en su interior." Se encontró que una de estas tumoraciones granulomatosas situada en el íleon terminal aproximadamente a 15 o 20 pulgadas de la válvula ileocecal estaba invaginada. Al no poderse desinvaginar se hizo la resección segmentaria obteniéndose una evolución satisfactoria.

Hay que hacer notar como en el tercer día postoperatorio, se presentó enfisema subcutáneo en la incisión y en ambas regiones inguinales. La placa simple de abdomen tomada el décimo día postoperatorio mostró la desaparición del pneumoperitoneo, sin existir aire subdiafragmático y sin visualizar quistes gaseosos. Tres meses y medio después de esta operación se hizo una segunda laparotomía por nueva oclusión localizada en el cuadrante superior derecho. El diagnóstico de la segunda oclusión intestinal se hizo cuatro semanas antes de admitirse la operación. Al ser operado el enfermo estaba en condiciones críticas. Los hallazgos operatorios fueron: Vólvulos del yeyuno adherente a la cara anterior del hígado.

El enfermo murió a las 14 horas de operado con falla coronaria aguda. La autopsia mostró estrangulación del asa aferente del yeyuno con torsión de su mesenterio. Es obvio que la estrangulación y torsión del yeyuno bajo el ligamento de Treitz no fué notada en la operación Esta zona está expuesta fácilmente al edema con interferencia vascular debido a la pequeña salida al rededor del ligamento de Treitz para el paso yeyunal y el acomodo del asa fija. En el estómago se encontró una estenosis pronunciada en forma de reloj de arena en la porción antral, como se muestra en las ilustraciones. La estenosis gástrica no fué reportada en las operaciones efectuadas en 1953 ni en Marzo de 1957. Durante la operación de Marzo de 1957 a pesar de que el estómago fué revisado, no se encontró la estenosis. La omisión fué debida sin duda a la gran cantidad de adherencias existentes en esa zona. Los estudios repetidos gastrointestinales no revelaron la presencia de estenosis gástrica, y por lo tanto las adherencias existentes en la región del antro no fueron tocadas. La principal obstrucción encontrada en la operación fué localizada en el íleon terminal. Por las malas condiciones del enfermo se aconsejaba un tratamiento quirúrgico corto.

Es evidente que aun encontrando la causa de

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una oclusión se debe hacer la revisión completa de todo el tubo digestivo, aún en el caso de que el estado del enfermo sea delicado. La observación cuidadosa efectuada durante el periódo de 3 y medio meses estableció en forma definitiva que la inanición es uno de los factores predisponentes a la pneumatosis. Aún más, puede concluirse que si se instala un regimen nutricional adecuado, puede controlarse el problema nutritivo y obtenerse una mejoría gradual del paciente.

Existe el hecho de que la pneumatosis puede desaparecer en forma espontanea yen nuestro caso, se presentó después de una resección segmentaria del ileon invaginado, sin tocar una estenosis gástrica existente, la que se localizó en forma accidental en la autopsia.

Refiriéndose a la etiologia de la pneumatosis intestinal y las teorías existentes, parece que existen factores mecánicos, nutricionales y químicos como determinantes en este cuadro patológico. La formación de quistes de gas es probablemente el resultado de una circulación linfática trastornada en todo el tubo digestivo. Los quistes gaseosos distendidos, morfológicamente, parecen formaciones linfáticas, y su contenido se deriva probablemente de una excesiva formación de bióxido de carbono.

Los cambios metabólicos y electrolíticos del aparato circulatorio son posiblemente responsables por los cambios osmóticos que se presentan en el tubo digestivo. Los cambios de presión en la red linfática del tubo digestivo en general, y la pared intestinal en particular, produce estancamiento linfático con edema, y la formación de un trasudado abdominal parecido al quimo. Esta condición es probablemente el resultado de una falla congestiva linfática producida por un aumento progresivo en la presión endolinfática, llegando al final a producir cuadros de hipertensión, parecido a la hipertensión pulmonar progresiva que produce una falla cardiaca congestiva.

Los síntomas mas comunes de importancia diagnóstica en la pneumatosis son: El pneumoperitoneo crónico, que es reportado con frecuencia y que en nuestro caso duró cuatro años. En el presente caso posiblemente existió el pneumoperitoneo cronico años antes de que fuera diagnosticado. Es evidente del estudio de la historia clínica de este enfermo y de otros, que la presencia de aire libre en el abdomen es uno de los síntomas diagnósticos precoces, antes de que aparezcan los signos clínicos. Es razonable pedir entonces que se busque la presencia de pneumoperitoneo aunque sea mínimo en los casos con trastornos intestinales indefinidos. La presencia de pneumoperitoneo sin shock y los demas síntomas alarmantes de una viscera hueca perforada, deben siempre hacernos pensar en pneumatosis. Las radiografías mostrando intestino en panal de abeja deben hacer sospechar la presencia de este padecimiento. La desaparición radiologica del pneumoperitoneo y los quistes fué confirmada en la segunda laparotomía, y debe considerarsele un metódo de confianza.

El caso presentado en este trabajo corrobora que se trata de un padecimiento crónico que puede continuar durante años. Se considera a la pneumatosis como un padecimento benigno, pero la posibilidad de una oclusión lo hacen más serio. El sitio donde se presentó la estrangulación de yeyuno con mesenterio torcido estaba libre de quistes de gas en la exploración de Marzo de 1957. Existe sin embargo la posibilidad de que existieran quistes gaseosos en la cara posterior del ligamento de Treitz o en la unión duodeno-yeyunal.

Siendo imposibles de localizar por la formación especial anatómica del igamento y funcionamiento de las visceras en ese lugar, la presencia de quistes gaseosos pudo producir interferencia circulatoria con el pedículo mesentérico yeyunal y por lo tanto con el yeyuno mismo, produciendo así el volvulus.

La primera oclusión aparente en Marzo de 1957 fué producida por un granuloma formado por quistes aglutinados, que se invaginó en la porción distal del intestino. La localización topográfica de la mayoría de los quistes de gas fué hecha en el borde antimesentérico, correspondiendo así a la distribución anatómica de los linfáticos.

El hallazgo invariable de células epiteliales forrando la pared de los quistes y la multiplicidad topográfica de las bulas, simulan sin lugar a duda la misma formación que los segmentos linfáticos. La presencia de ascitis de consistencia espumosa parecida a la glicerina, encontrada en el caso descrito fué observada también por otros investigadores, aunque ellos no hacían notar ni su consistencia ni lo espumoso del líquido.

RESUMEN

1. Se presenta una revisión de la literatura mundial sobre Pneumatosis Intestinorum Hominis, con un caso clínico. Se presenta rara vez en el hombre y es de origen desconocido.
2. Como resultado de esta condición patológica se forman quistes de gas en la serosa visceral del intestino y a traves de la mucosa. Se encuentra además un exudado aceitoso espumoso.
3. El padecimiento es crónico, de duración exageradamente larga, progresando lentamente, causando emaciación, invalidez y cambios en la personalidad. Los síntomas son de obstrucción intestinal crónica progresiva.
4. Se exploran las teorías etiológicas. Se formula una hipótesis sobre hipertensión linfática.
5. La resección segmental del ileum terminal invaginado, resultó util para contrarrestar la formación de quistes y para mejorar el estado general del paciente.
6. Tuvo que operarse en forma retardada tres meses mas tarde, por causa del enfermo, de un cuadro de estrangulación yeyunal, más allá de los límites de seguridad.
7. La autopsia mostró buenos resultados de la primera operación y reveló la estrangulación del yeyuno. Se hizo un diagnóstico de presunción de accidente cerebro-vascular, anterior o simultaneo al acto quirúrgico.

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THE PUBLISHER SPEAKS

By J. N. McMeekin,
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To The Members of the
ARIZONA MEDICAL ASSOCIATION, INC.

Fourteen years ago, at the request of the late and beloved Dr. Frank J. Milloy, then secretary of the Association and editor of the Journal, I accepted the responsibility of publishing ARIZONA MEDICINE. With this issue I am turning it back to the Association.

As Dr. Milloy told me at the time, it was a pretty sorry publication. The medical content was good, of course, he saw to that, but as there was no business management the advertising support was scanty, local, and amounted to practically nothing. It was supposed to be a bi-monthly at that time, and it did come out occasionally, when the weather was favorable and the printers could find nothing else to do.

Dr. Milloy figured, correctly, that with his medical editorial know-how, combined with my business know-how, working closely together, we could develop ARIZONA MEDICINE into a first-class publication that would be a credit to the profession.

And that is exactly what happened. All down through the years Dr. Milloy, and his successor as editor, Dr. R. Lee Foster, worked closely with me in building up this publication, until it came to be recognized as one of the finest medical journals published in the United States. It has repeatedly been given high place by national organizations, and the top place of "First In General Excellence" among Arizona magazines.

From a scrawny little publication that happened once in a while it was developed into a high quality monthly that carried a tremendous volume of national pharmaceutical advertising that was interesting and helpful to your members in keeping abreast of the latest developments.

How much time and money I spent, how many national and regional conventions I attended, how many trips for conferences with the agencies—how much and how many I could dig out of our books—but the point is that I got the job done because I know how, and because for many years I had the complete cooperation of the editors and the publication committees.

Together we developed a splendid publication, with sufficient income to pay all the costs of publication, all the costs of securing the business, and all of the costs of supplying the magazine to your membership, the membership of your auxiliary, and world-wide exchange with other medical organizations and publications.

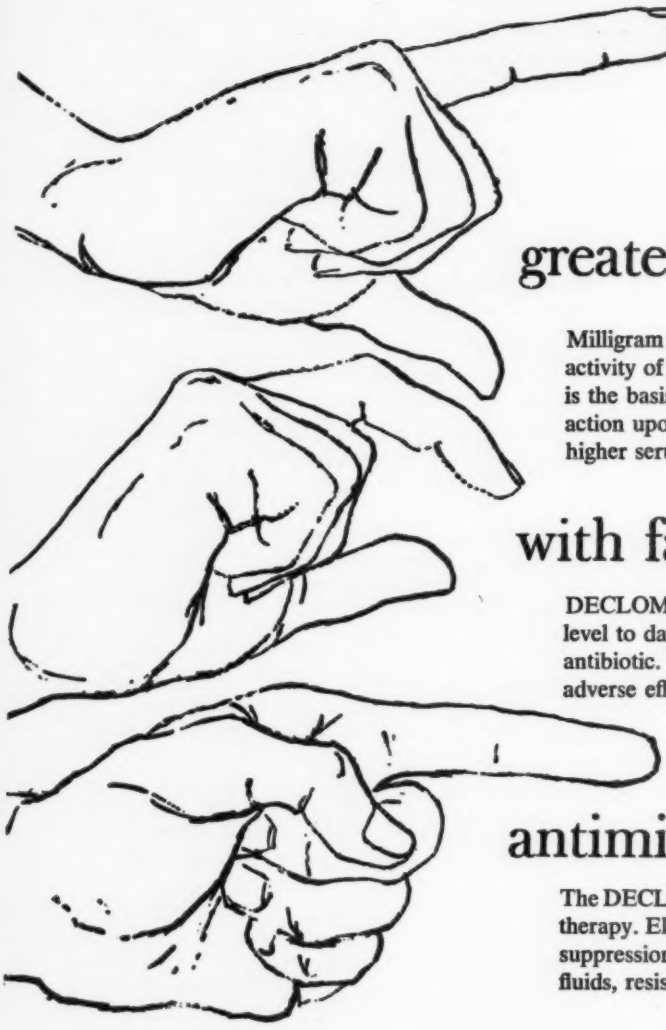
All this changed when the present editor took over. He has never called at the publication office, never offered to cooperate with me in getting out the best possible publication. He has never attended meetings, never called any meetings of the Publication Committee, and his scanty knowledge of the publication field has been reflected in material sent me to fill space in the magazine. I have been reluctantly compelled, when asked about the useless re-publication in ARIZONA MEDICINE, of material every doctor had already seen in his national publications, to confess that I had no opportunity to confer with the editorial staff, or to make or receive constructive suggestions. Under such circumstances it was inevitable that the quality of the publication suffered.

Meantime a member of your State Association staff seems to have been promoting himself and his ideas—although he has had no training or experience, or even contacts, in the publication field, and knows nothing whatever about advertising—and, incidentally, gave your Journal staff little support in our efforts to concentrate National Advertising support behind your state Journal.

(Continued on Page 814)

LEDERLE INTRODUCES...

a masterpiec



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DECLOMYCIN demonstrates the highest ratio of prolonged act level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents.

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*Hirsch, H. A., and Finlan *New England J. Med.* 26 (May 20)

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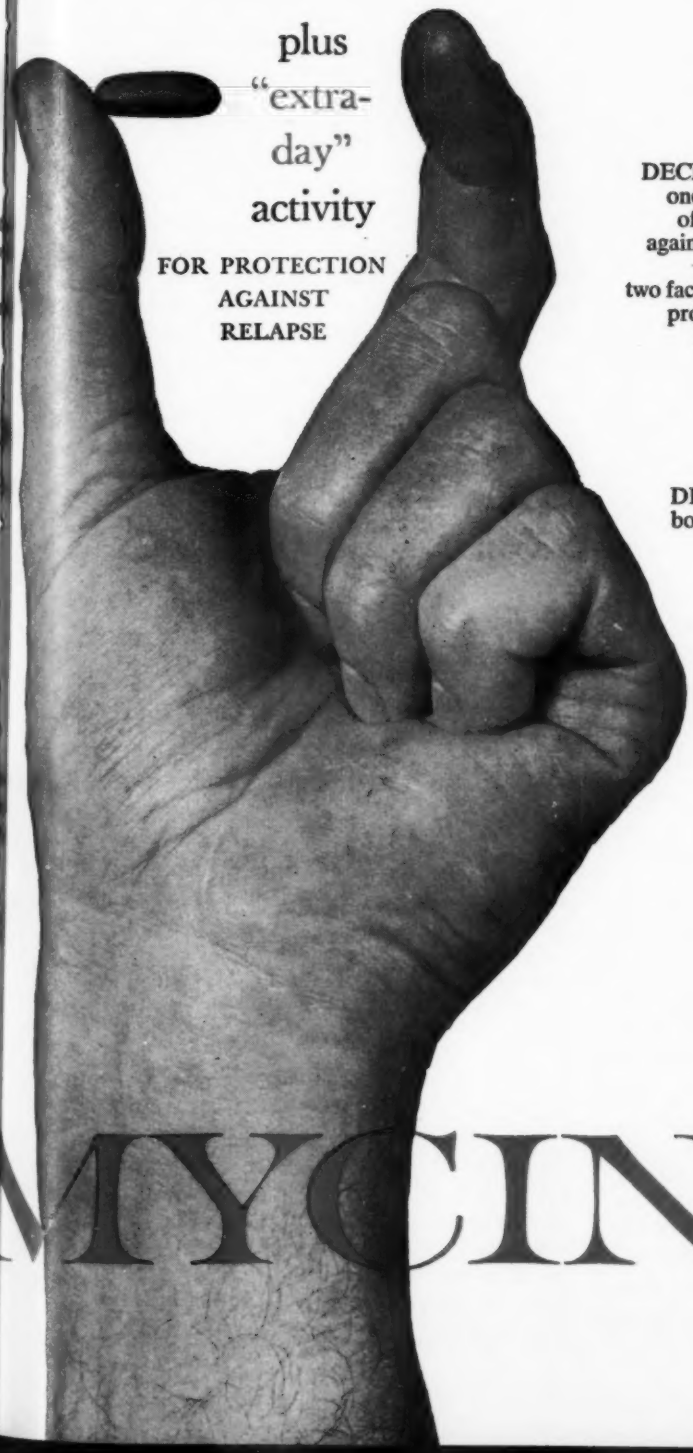

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Editorial Section

ARIZONA MEDICINE

Journal of

The ARIZONA MEDICAL ASSOCIATION, INC.

VOL. 16 DECEMBER, 1959 NO. 12

CONTRIBUTORS

The Editor sincerely solicits contributions of scientific articles for publication in ARIZONA MEDICINE. All such contributions are greatly appreciated. All will be given equal consideration.

Certain general rules must be followed, however, and the Editor therefore respectfully submits the following suggestions to authors and contributors:

1. Follow the general rules of good English, especially with regard to construction, diction, spelling, and punctuation.
2. Be guided by the general rules of medical writing as followed by the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.
3. Be brief, even while being thorough and complete. Avoid unnecessary words. Try to limit the article to 1500 words.
4. Read and re-read the manuscript several times to correct it, especially for spelling and punctuation.
5. Manuscripts should be typewritten, double spaced, and the original and a carbon copy submitted.
6. Articles for publication should have been read before a controversial body, e.g., a hospital staff meeting, or a county medical society meeting.
7. Exclusive Publication—Articles are accepted for publication on condition that they are contributed solely to this Journal. Ordinarily contributors will be notifed within 60 days if a manuscript is accepted for publication. Every effort will be made to return unused manuscripts.
8. Illustrations — Ordinarily publication of 2 or 3 illustrations accompanying an article will be paid for by Arizona Medicine. Any number beyond this will have to be paid for by the author.
9. Reprints — Reprints must be paid for by the author at established standard rates.

The Editor is always ready, willing, and happy to help in any way possible.

(The Opinions expressed in original contributions do not necessarily express the opinion of the Editorial Board.)

A REPORT TO THE MEMBERSHIP FROM THE PRESIDENT

AS PRESIDENT of your association, I presume you might ask me to review those activities that might affect each one of you personally. One pertinent question seems to be a recurrent theme. It can be stated as follows: "What is the state medical association doing for me that will justify the dues I am compelled to pay?" Ordinarily, the answer to this often becomes detailed and may prove unsatisfactory. I have, however, prepared myself this time by having Mr. Robert Carpenter and Mr. Paul Boykin compose a five page letter. I have it in hand at this time. I am ready to go over it in detail with you any time you so desire. I know that one time or another in the course of our medical life in our respective communities, each one of us feels that the state association dues are too high and could be reduced if only the powers that be would disengage their big, fat derrieres from the security of the administrative chair and get the job done. I also am positive beyond a shadow of a doubt that these ideas change as one pursues them from the land of imagination into the land of reality. As president of the Maricopa County Medical Society in 1951, one of my pet projects was to find out just what the state association was doing with our money. There is a letter in the file of the state medical association office wherein I demanded detailed and specific accounting, not only for finances, but for activities. This request received prompt attention as well as an invitation to meet and discuss problems of mutual interest and importance to both organizations. Thus began the education of the belligerent neophyte. You, too, can be educated if you keep your mind open and your arguments logical.

The crux of this situation, and one we must all recognize, is the fact that your state organization is dedicated to two prime concepts: One, the preservation of the practice of medicine as you now know it. Two: The maintenance of the dignity and hard-earned reputation of each physician as an individual. Much activity and no small amount of money is necessary to live up to these concepts. Your fellow colleagues labor long and hard to see these things acomplished

for you. I do it, and your colleague does it willingly because we know that your turn is coming, just as our turn followed our esteemed predecessors'. It requires many hours of committee work plus individual effort, and this calls for a certain amount of dedication. If there arises in your mind a resentment or a disagreement regarding what the state association does or does not do, please stop growling in your beard and do something about it. Put your fighting togs on and have at it. I would caution you, however, to come to the wars well prepared. Your pet project or your brilliant ideas may have been reviewed and found wanting, or already discussed and discarded. I would also like to predict that for every constructive criticism which is implemented by a man of good intentions, on that day is born a new member of the "Old Guard" of our association. Once you determine to find the facts regarding your state association, you are destined for some pleasant surprises. You make friends among your colleagues outside of your everyday environment. The work is pleasant, though sometimes tedious. Of paramount importance, you finally and forever see that the state association backstops each and every physician in maintaining and preserving the high ideals of our distinguished profession. One of the most rewarding surprises is to find the unusual efficiency and co-operation of the executive secretary and his management of the central office of the association. We are indeed fortunate to have in our employ Mr. Robert Carpenter and Mr. Paul Boykin. I will not elaborate, but I invite you to keep this in mind as you progress in any inquiry you care to make. Sooner or later you will give a loud amen to the opinion just expressed.

Special Mention

I have one topic that deserves a special mention. Your respective county societies have been active in programs of better public relations. The main objective has been to carry this to the point of guaranteeing our patients medical care second to none. We have been of the opinion that misunderstandings, and especially unwarranted criticisms of doctors could be nipped in a bud with proper and early attack on the problem at its source. I am not going to discuss the progress of these programs, as it properly belongs in the reports of your respective county presidents. I mention it only as a background in order to elaborate on a new and nationwide concern regarding our inter-professional problems. The American Medical Association is concerned. We in Arizona have been more cognizant each year of the necessity for better discipline among the members of our profession. You, of course, are aware that the grievance committee or the board of medical examiners as a rule can adequately handle any problems that arise regarding questionable practice by one of your colleagues. This is well and good, but what do we do about one of our fellow practitioners who is not a member of our medical association? The answer is that we do nothing. If we sit by with folded impotent hands, who carries the ball? The board of medical examiners is specifically charged with this responsibility, say you. The board of medical examiners does a yeoman-like job, make no mistake about that, but in certain instances they cannot operate in an effective manner. This hiatus must be bridged. One solution has presumably been to admit a questionable character to membership in the respective county associations in order "to make a good boy" of him. To this concept I am in entire and complete disagreement. A bad apple in a barrel of good apples spoils the good ones, but does not alter the putrefaction or stink of the bad one. Fortunately, we do not have too many bad apples to worry about. I do believe, however, that admission of a member to an organization such as ours demands thorough investigation. If a candidate has a preceding bad reputation, it should be discovered and the facts made an integral part of his record. The board of censors of each county society is the screening body for new applicants. In my term on the board of censors I am unhappy to have to confess that the scrutiny of the applicant was often cursory. I also remember the sticky problems we occasionally had. I recall very distinctly how we got the monkey off our backs by passing the buck to the county society as a whole. I now believe that this is not proper. If a bad apple is recognized by the board of censors, his admission or rejection should not be foisted off on the society as a group simply as a buck-pasisng maneuver. If, however, the board of censors can justifiably persist in this attitude, then they must also be prepared to present the picture in its true perspective so that the members may vote intelligently. This often creates quite a hassle that could have been settled quietly at the board of censors level. Please keep in mind that the "temporary" or term membership at the county level was not set up with the orig-

inal intent to make good apples out of bad ones. This mechanism was instituted in order to be able to find the occasional individual who by some happenstance might make the first hurdle into temporary membership smelling like a rose. If he later bloomed in a decadent splendor of undesirable, unethical conduct, he could be eliminated from consideration for permanent membership. If we do reject an applicant early in the game at the board of censors level, he presumably is beyond control. What are we to do if this individual then proceeds to practice a type of medicine we all recognize as incompetent, dishonest, or unethical? Some one or a few of us could rise in all of our individual or collective wrath and take care of the problem. The only practical disadvantage of this, however, is that he who leads such a punitive action often finds himself out on a limb. Soon he feels very sorry for old Number One. Some lawyer with a sense of humor may inform this Don Quixote that activities of a punitive nature may be subjected to legal action by the individual in question. At this stage, old Number One is very envious of the Arab of antiquity who quietly folded his tent and silently stole away. I firmly believe more of us would be willing to take on these disciplinary problems if we knew we had solid backing in the form of some law that would fortify our efforts and prevent us from being put upon by legal action, threatened or real. The solution to this problem may be found in the statutes of the State of Washington. A disciplinary board has been set up and legislative action has resulted in a law which puts teeth and protection into the actions of individuals who would safeguard the public from unscrupulous practitioners. The American Medical Association is looking into this subject. You may have noted mention of it in the Journal of the American Medical Association. We will hear more about it in the future. In the meantime, let us all call a spade a spade, and accept as members only those fully deserving of the honor.

Medical Education

I would like to make mention of our effort at the last state association meeting to present for you a full day session on medical education. The September and October issues of your state journal, *Arizona Medicine*, contained the papers presented at Chandler last May. In November all of these papers were made available to you in booklet form. It should give all of you a handy reference to a well rounded discussion on medical education. I trust you read the papers closely and digest them well.

The importance of medical education to the State of Arizona has resulted in the appointment of a Committee on Careers by your state organization. I will not bore you with my thoughts on the value of this committee. The November issue of *Arizona Medicine* has an article entitled, "Medical Manpower for Arizona." This is an effort to bring to you a summary of where we are now in medical education in Arizona, and how we are going to proceed in the future to obtain sufficient medical manpower for our state.

I now have a pleasant duty to perform in calling to your attention the fact that the Arizona Medical Association has had the honor of national recognition on at least two counts in the past 12 months, and is looking forward to additional recognition in the near future.

Dr. Jess Hamer has just completed his term as vice president of the American Medical Association. We are proud of this well deserved honor being bestowed on one of our members and we congratulate him.

Dr. Harold Kohl has brought the name of the Arizona Medical Association before the eyes of our colleagues throughout the nation. Dr. Kohl originated the plan for financial assistance to our nation's medical schools now known officially as "The Arizona Plan." In brief, it is a method of directing gifts from the pharmaceutical association into the funds for medical education of the American Medical Education Foundation. Instead of sending you a gift at Christmas time, the pharmacists have been convinced that you and I would be much happier if this gift was sent in the form of money to help our medical schools. This idea of Dr. Kohl's promises to be of tremendous financial help to our medical schools, and emphasizes again the interest the Arizona Medical Association has in medical education. Our thanks and appreciation to Dr. Kohl.

It is with some interest that I have watched the development of "The Pima Plan" and its method of handling the medico-legal malpractice problem. The Pima County Medical Society has had this particular panel in operation now for approximately two years and the experience is quite encouraging. This plan has been discussed before a number of medical groups, and is meeting with favor not only in Arizona but in other parts of the country. Our congratulations

to the Pima County Medical Society and their friends in the legal profession who have brought about this very commendable innovation.

Finally, I would like to call attention to the fact that our journal, *Arizona Medicine*, is to be published by the state association beginning Jan. 1, 1960. The central office will handle the business and advertising aspects of the operation. Dr. Darwin Neubauer, in conjunction with the publishing committee and the central office staff, have been presented with many problems and much time and effort has been expended in order to make the transition proceed smoothly. We are looking forward to the "new" *Arizona Medicine Journal* with expectation and unbounded confidence that it will be outstanding and a journal you will be proud to receive. We are even optimistic enough to hope that revenues will be forthcoming that will assist in the ever increasing expenditures necessary to conduct activities on the state level.

$$$$$$ $$$$$$ SERVICES CASH $$$$$$ $$$$$$

THE MILWAUKEE Labor Press recently stated, ". . . many doctors have made an exact science out of squeezing the last nickel from their patient." This is an example of how we physicians are being harassed, by many sources, about our "poor public relations." Many attempts have been made individually, and as organized medicine, to study the charges and to correct our deficiencies, but the bombardment continues. We should do three things:

First, we should ascertain wherein we are wrong and then take firm steps to permanently correct our errors.

Second, we should go all out, by public education, to prove that many of the accusations are wilthout merit.

Third, we should inventory our doings, to ferret out that which might further kindle the public's ill-will. It is onerous that this ill-will has been kindled to a degree which frustrates the honorable physician.

A few years ago, a sardonic joke among the physicians of Arizona was that a group of doctors had a cash register prominently displayed, so that it was the first thing a patient would see on entering the office. I am not sure that such a mercenary device is being used today, but I do know that tactics equally as repulsive are being employed.

There is one thing which has not been widely publicized as yet, namely, the display of signs, by some doctors, about the payment of bills. We should consider the full impact of such signs as: *All Services Cash – All Services Cash Unless Otherwise Arranged – Please Pay Cashier – Please Make Arrangements for Payments at the Desk – Member of ..... Credit Bureau.*

These signs, or variants of the same, are being displayed by some physicians. Thus the $$ sign becomes mixed with the patient's desire for relief from some affliction, even before he has been extended the "courtesy" of registering, or meeting the doctor.

When Business Isn't Business

The registration continues the same affront, in that the questions include a statement as to the name of the bank in which the patient keeps his checking account, and the name of the insurance company (if any) which might be expected to pay the bill. Some of our physicians are more subtle and do finish their examination before they hand the patient a slip of paper which reads . . . *"Please pay $$$ to the girl at the desk."*

Our "good" business advisors have told us that it is good business to do everything possible to collect all the $$ we can, by most any method which might be successful at the moment. Business is business, but what we have to decide is whether we physicians are primarily interested in our profession as a profession, or in our profession as a business.

If we act to much like we are engaged in a business, then we must expect to have even less respect from the public than they extend to business men, because we wear the cloak of a profession and hence we are guilty of duplicity.

Have we forgotten the Golden Rule? When a patient selects his doctor and submits to his advice and treatment, he must have implicit confidence, because it is his life and not material things which he has entrusted to the doctor. For anyone who trusts us with his intimate secrets and his life, it would indeed seem that the least we could do to reciprocate would be to trust them, for a little while, for a few $$$$.

The prominent display of signs, which infer that all people are deadbeats, merely incites a desire in thinking persons to help prove that your insinuations are correct. To do so, they just make the $$$ harder to collect. About 2 or 3 per cent of all people are deadbeats and considerable more are just borderline deadbeats, who are looking for any affront which might justify their own desire not to pay $$$$. It is only the deadbeat and the moron who are not offended by the doctor who puts the $$$$ sign in first place, ahead of professional service.

If we doctors spend ample time in giving quality medical care, in such a fashion that our patients are convinced that we have done our all, they will be much more apt to show their gratitude with a check.

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Clinical reports on Dartal: 1. Edisen, C. B., and Samuels, A. S.: A.M.A. Arch. Neurol. & Psychiat. *80*:481 (Oct.) 1958. 2. Ferrand, P. T.: Minnesota Med. *41*:853 (Dec.) 1958. 3. Mathews, F. P.: Am. J. Psychiat. *114*:1034 (May) 1958.

SEARLE

Topics of Current Medical Interest

THE ARIZONA MEDICAL ASSOCIATION, INC.

PROFESSIONAL COMMITTEE

MEETING OF the professional committee of The Arizona Medical Association, Inc., August 9, 1959.

Present: Drs. Farness, Orin J., Gregory, T. Richard, Johns, Richard B., Kinkade, Joseph M., Leonard, Robert B., Schwartzmann, John R., Chairman; Stapley, Lorel A., Secretary; Wormley, Lowell C.

Staff: Boykin, Paul R., Assistant Executive Secretary; Carpenter, Robert, Executive Secretary.

SUBCOMMITTEE ORGANIZATION

With the adoption, by the house of delegates of the association of a completely modified and amended by-laws, it became necessary to revise and in some instances consolidate the subcommittee structure and chairmanship assignments of the professional committee. Following is listed the classifications and appointments for the fiscal year 1959-60:

Aging.....Lowell C. Wormley, M.D.
Cancer.....Robert B. Leonard, M.D.
Civil Defense & Safety (To Be announced).

Note: Need for appointment of an additional member to the professional committee was determined and it was directed that the president be so informed. The name of John W. Kennedy, M.D. (Phoenix) was suggested.

It was further determined that matters dealing with air pollution shall be considered a part of the scope of activity of this subcommittee.

Crippled Children.Thomas H. Taber, Jr. M.D.
General Medicine.....Orin J. Farness, M.D.

Note: It was determined that matters dealing with poisoning control and tuberculosis shall be considered a part of the scope of activity of this subcommittee.

Hospital & Nursing Problems—Joseph M. Kinkade, M.D.

Note: It was determined that matters dealing with hard of hearing shall be considered a part of the scope of activity of this subcommittee.

Maternal & Child Health — Richard B. Johns, M.D.

Mental Diseases—T. Richard Gregory, M.D.
Rehabilitation—Ray Fife, M.D.
Venereal Diseases—Laddie L. Stolfa, M.D.

It was determined to eliminate the subcommittee on seminars; likewise, it was determined the present need for subcommittees on blood bank (this to come under the medical economics committee) and medicare adjudication (this also to come under the medical economics committee) is not indicated.

TRANSFER OF PREPAID MEDICAL SERVICES

It was again reported there had been no further response from the pathologists referable to previous discussions in the matter of suggested transfer of prepaid medical services from Blue Cross to Blue Shield.

It was moved, seconded and unanimously carried, since there has been no further activity in this regard, that the matter be dropped without reaching any decisions; that the pathology group be so informed; and should the pathologists wish this professional committee to again consider its problem at some future date, that they so advise after they have prepared for it.

SUBCOMMITTEE REPORTS

Aging:

Doctor Wormley reported that, with recent additions, his subcommittee on aging will comprise the following membership, listing the titles of subjects or fields each is to become conversant with, in association with the problem of aging from the medical viewpoint:

Drs.: Counseller, Virgil (Phoenix)—"Utilization of Professional Skills of Older Persons"; Eckstein, Albert (Phoenix)—"Nursing Homes and the Medical Care Program as it Exists Today for the Older Person"; Gotthelf, Edward J. (Tucson)—"Specific Medical Problems of Aging"; Hamer, Jesse D. (Phoenix)—"Current Activity in the Field of Aging"; Holsey, William F. (Tucson)—"Surgical Problems of Older Individuals"; Jarrett, Paul B. (Phoenix)—"The Hazards of Accidents in the Older Person"; Joseph, Samuel R. (Phoenix)—"Hospitalization Insurance Problems for the Aged"; Schell, Donald E. (Tucson) — "Home Programs in Anticipation of Retirement and the Financial Responsibility of the Family and the State for the Senior Citizen"; Smelker, Van A. (Tucson)—"The Role of National Wel-

fare and Foundations in the Directions of the Care of the Aged and Aging"; Wick, Samuel (Phoenix)—"A Program for the Continued Mental Activity and Like Interest in Older People."

Doctor Wormley then proceeded to abstract items of special interest and activity since the last meeting of this committee, including, but not limited to: (a) national conference of the Joint Council to Improve the Health Care of the Aged held in Washington, D. C.; (b) National Leadership Training Institute held in Ann Arbor, Mich. (each attended by Doctor Hamer, representing the association, who is to be invited to attend the next meeting of this committee and report); (c) HR 4700 (Forand bill) hearings before the ways and means committee of the U. S. House of Representatives in Washington, D. C., the week of July 12, Doctor Hamer in attendance; (d) voluntary health insurance plans for individuals over the age of 65 being developed by private insurance carriers, including Blue Cross-Blue Shield; (e) continuing need for organization of county medical society committees in the field of aging; (f) statistical reports of the Rhode Island Medical Society, and the Health Insurance Association, relating to progress in the field of care for the aged; (g) AMA field service report on the activities of the senate McNamara committee to study the problems of the aged and contemplated survey in selected key cities.

Discussion ensued with emphasis on the established philosophy that we will learn all we can; reasonably assist and co-operate, but hold unbridled enthusiasm to the point where we see our way clear to justify pursuing a course of action; reach our own decisions based on the merits; continue encouragement among private insurance carriers, Blue Cross and Blue Shield, to extend coverage to include older groups, 65 and over; consider the needs of the aged who are bedridden or disabled, and who could be cared for outside the hospital in nursing or rest homes, or in the home itself; study the possibilities of vocational rehabilitation, providing work for those capable thereof – thus improving the health and mental attitudes of the aged; and oppose the philosophy of the Forand measure.

It was moved, seconded and unanimously carried that the professional committee, after extensive study and evaluation of the provisions of HR 4700, 86th congress, more frequently referred to as the Forand bill (which amends the Social Security Act to provide hospital, surgical and nursing home treatment for eligible beneficiaries, principally those over 65 years of age) and examination of the facts, strongly recommends to the board of directors that this association continue actively its opposition to this proposed measure as an impractical and impossible solution to the problems of the aging; and that the congressional delegation representing this state be adequately so informed.

It was moved, seconded and unanimously carried, after careful consideration of the steady increase in acceptance by medical societies thorughout the country (now totalling 25 out of the 48 state societies) of the theory of "voluntary insurance" as a means toward meeting at least some of the health needs of the aged, and inasmuch as the professional committee feels that it is a fair and equitable way of financing the hospital and medical care of the older individuals, that it be the recommendation of this committee that the state association continue acceptance of and further encourage the development and/or extension of voluntary private and Blue Cross-Blue Shield health insurance programs to include individuals 65 years of age and over, even to the extent of providing coverage for rest home or nursing home care as well as for care in the home itself.

It was moved, seconded and unanimously carried that the professional committee reiterate its continuing philosophy of conservation in approaching the problems of the aging, as previously declared and presented to the board of directors.

Air Pollution:

No report; however, hereafter, this activity will be combined with the subcommittee on civil defense and safety.

Cancer:

The Arizona Academy of General Practice reported that requirements for Category 1 credit for any seminar, symposium, or medical meeting include: (1) it must be an Arizona Academy of General Practice co-sponsored meeting; (2) there must be at least one member of the AAGP active on the program committee; and (3) application for Category 1 credit must be made directly to the secretary of AAGP, who will institute the necessary papers for formal approval.

The Arizona Division of the American Cancer Society requests approval of this committee of its annual cancer seminar to be held at the Ari-

zona Biltmore, Phoenix, Jan. 14, 15 and 16, 1960. Doctor Leonard further stated that there would be no invitations extended to doctors of osteopathy to attend the siminar.

It was moved, seconded and unanimously carried that this professional committee recommend to the board of directors and urge the association's co-sponsorship of the eighth annual cancer seminar to be held at the Arizona Biltmore, Phoenix, Jan. 14, 15 and 16, 1960, with the assurance that such association sponsorship does not require any financial obligation.

For the information of the committee, Doctor Leonard presented for review a form of report to be used by the Federated Business and Professional Women's Clubs in association with its contest program to encourage members to seek a general physical examination by their individual physicians as a preventive measure against cancer. This report form has been developed for the use and convenience of the physician, the club receiving only that portion, signed by the physician, to the effect that the individual has received an examination, and without further detail.

Status of the proposed tumor registry was also reviewed by Doctor Leonard, following defeat of enactment of a law during the last state legislative session which would have required such reporting. The required use of names was the principal objection. This association subsequently withdrew its support and urged the cancer society to give continued study to the possibility of achieving the objective through other means or method.

Civil Defense:

This subcommittee on civil defense and safety (combined) will be organized and a report will be expected at the next meeting.

Crippled Children:

In the absence of Doctor Thomas Taber Jr., who will head this subcommittee, no report was presented. Doctor Schwartzmann stated that there had been and will be continuing activity in correlating and tabulating facilities that are presentely available for the care of crippled children and on completion it will be adequately publicized.

General Medicine:

Doctor Farness reviewed the report on osteopathy, prepared by Doctor Jesse D. Hamer, Arizona (association) delegate to AMA, the outcome of deliberations of the AMA House of Delegates in annual meeting recently concluded in Atlantic City. The following policy in regard to the relations between doctors of medicine and osteopaths was adopted:

"All voluntary professional associations between doctors of medicine and those who practice a system of healing not based on scientific principles are unethical.

"Enactment of medical practice acts, requiring all who practice as physicians and surgeons to meet the same qualifications, take the same examinations and graduate from schools approved by the same agency should be encouraged by the constituent associations.

"It shall not be considered contrary to the principles of medical ethics for doctors of medicine to teach students in an osteopathic college which is in process of being converted into an approved medical school under the supervision of the Council on Medical Education and Hospitals of the American Medical Association.

"That a liaison committee be appointed by the board of trustees of the American Medical Association to meet with representatives of the American Osteopathic Association, if mutually agreeable, to consider problems of common concern including inter-professional relations on a national level."

Also reviewed was a medical opinion of a pediatrician and an allergist concerning benefit of Arizona climate in the treatment of infectious asthma in children based on experience and records of the Asthmatic Foundation in Tucson, which was developed to satisfy inquiry received from Robert S. Causey, M.D. of Marietta, Ga.

Another matter of long standing and controversy discussed was the treatment of scorpion sting by Herbert L. Stahnke, Ph.D., director of Poisonous Animals Research Laboratory, Arizona State University, Tempe, and application pending for a federal (Division of Biologics Standards, National Institutes of Helath, HEW) license for the manufacture and sale of scorpion anti-venom. Reference was made to a recently published article appearing in *Arizona Medicine*, July issue, by Henry P. Limbacher, M.D. (and Charles H. Lowe Jr., Ph.D.) entitled: "The Treatment of Poisonous Bites and Stings," pointing out possible damage to tissue in certain cases caused by drastic tissue refrigeration, etc. Interest in and work of Frederick A. Shannon, M.D. of Wickenburg in the matter of poisonous bites was likewise referred to and obvious need

for authentic information dealing with the therapeutic aspects of medical management indicated. It was directed that Doctor Farness, as chairman of this subcommittee on general medicine, undertake the project of correlating all available material and experiences in Arizona, referable to the treatment of poisonous bites, confer with both Doctors Limbacher and Shannon and any others, and formulate a report that will be both informative and useful to the profession and other interested parties in this regard.

Hard of Hearing:

No report. This activity will hereafter be included in the scope of operations of the subcommittee on hospital and nursing problems under Doctor Kinkade.

Hospital and Nursing Problems:

It was determined that inasmuch as Doctor Norman A. Ross, former chairman of this subcommittee, is no longer a member of the professional committee, Doctor Kinkade, now chairman, will be part of and assist the special committee previously appointed, including Doctor Gregory, as chairman, and Doctor Leonard, in the matter of inspection of the North Mountain Hospital, Phoenix.

Maternal and Child Health:

Doctor Schwartzman reported that possibly the most recent activity in this field has been the polio immunization drive supported by this committee and finally the National Foundation. With the co-operation of the county societies, progress is being made.

Doctor Johns called attention to the previous action of the house of delegates of this association in meeting held May 2, 1959, at which time a resolution was adopted dealing with the treatment of the eyes of the newborn, requesting the Arizona State Department of Health to approve a list of additional agents other than silver nitrate for the prevention of gonorrheal ophthalmia of the newborn, after consultation with recognized medical authorities on the subject. Doctor Salsbury reported that about two years ago, effort was made to obtain an expression of opinion from pediatricians and obstetricians; however, about a year ago the pediatricians in this area voted against the use of anything except silver nitrate, recommended also by the American Academy of Pediatrics. The Graham County Medical Society recently approved that an additional list of drugs other than silver nitrate be published. Obviously, there is a difference of opinion and any change now would only confuse the issue. There appears to be no serious complications resulting from the use of silver nitrate, and yet there are problems involved in the use of other drugs i.e., development of sensitivities, producing antibiotic resistance in the newborn in nurseries, etc. Further study and recommended action will be taken up at the next meeting.

Mental Diseases:

Doctor Gregory recommended favorable consideration be given the proposed WICHE postgraduate clinical psychiatry regional program for non-psychiatric physicians. While there are differences of opinion among certain of the psychiatrists as to the value of such program, the board of directors be informed that the committee feels the proposal has sufficient merit to approve of a pilot program to be undertaken in co-operation therewith; further, it is understood that such participation will entail no financial obligation on the part of the association. In view of the fact that the board is not scheduled soon to meet, it was further requested that the president, Doctor Melick, be informed of this action, inasmuch as time appears to be of the essence in setting up such a program, should it be approved by the board.

The sixth annual conference on mental health, sponsored by the American Medical Association's Council on Mental Health, was held in Chicago at the Drake, Nov. 20 and 21, 1959. Doctor Gregory attended this meeting representing the association. Doctor Gregory is preparing a report for publication in *Arizona Medicine* on those aspects of the general meeting which will be of particular interest to the membership at large, and in addition, inform the psychiatrists of this state regarding those portions of primary interest to its specialty field.

Poisoning Control:

No report. Such activity will be absorbed by the subcommittee on general medicine.

Rehabilitation:

In the absence of Doctor Fife, no report was presented. Doctor Schwartzmann indicated that he anticipated activity in this field will assume major proportions in the months ahead, even surpassing those in the field of aging and the aged. He urged each member to be alert to the problem and render every assistance to Doctor Fife, subcommittee chairman, who already has become involved therein.

Safety:

"Safety" will be combined and hereafter included in the scope of operation of the newly activated subcommittee on civil defense and safety.

Seminars:

The subcommittee on seminars will be eliminated for the time being, a member of this professional committee having been appointed to serve on the scientific assembly committee whose interests are similar.

Tuberculosis:

This activity hereafter will be absorbed by the subcommittee on general medicine; however, Doctor Farness, former subcommittee chairman, reported on the recently concluded tuberculosis nursing conference, with emphasis on thoracic surgery, held Aug. 3 through 7, 1959, at the University of Arizona, Tucson, providing nurse training on the university level. The participants were outstanding, the program well conducted, and it was recommended and ordered that a letter be prepared and forwarded to Mrs. Pearl Parvin Coulter, Director of the School of Nursing, U. of A., expressing appreciation for her efforts in conducting the seminar.

Venereal Diseases:

No report.

COMMUNICATIONS

None presented.

(Continued from Page 797)

Long before your last State Meeting your state secretary informed me it would be useless to expect a renewal of our publishing contract, as the Journal would be handled out of the editor's Tucson office, through the University of Arizona press bureau.

I am not in the least disturbed that this hired help has persuaded a few doctors and a few professors at the University of Arizona to "take a whirl" at publishing ARIZONA MEDICINE. I just feel sorry about what will undoubtedly happen to the beautiful publication to which I and my staff have devoted so much time, money, work, and know how.

Miss Hilda Wax, who has been my assistant for 11 years, Mr. Julian De Vries, my proof reader and advisor, Mr. A LaBenz, commerical artist who has been doing my art work for 10 years, Mr. Jackson, in charge of National Advertising in Chicago.

I have a shrewd suspicion that the experimenting of the new staff will be interesting to all observers, probably diverting, and possibly even amusing. Other similar experiments have been observed, where there was a similar lack of experience and training, to have been quite generally unfortunate.

(Continued on Page 816)

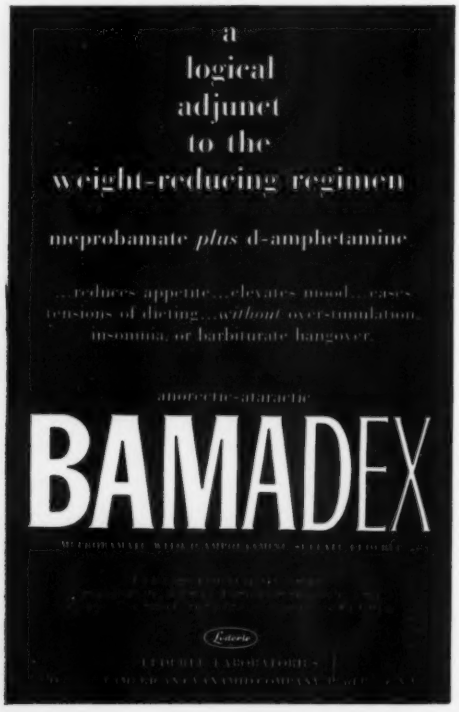
(Continued from Page 814)

Meantime I shall carry on my business of "official publications," as I have been doing for twenty years; and it might even happen, at some future time, that I might again have the opportunity to be of service to the medical profession of Arizona.

To the many members of your Association who have worked with me in the tremendous development of ARIZONA MEDICINE while under my management, I extend my sincere thanks and highest personal regards, and the Season's Greetings.

Sincerely,

John N. McMeekin,



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PROGRAM

January 12, 1960 – "Chronic Ulcerative Colitis" Dr. Robert T. Tidrick, Professor of Surgery and Chairman of the Department, University of Iowa.

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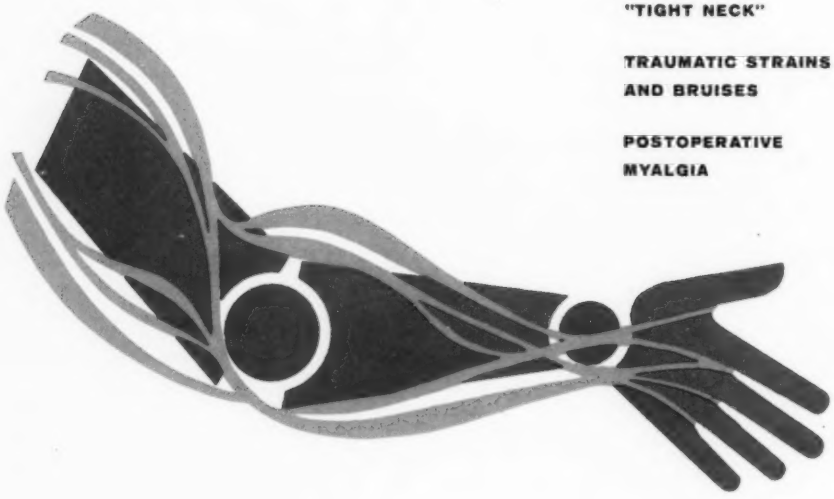

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FROM
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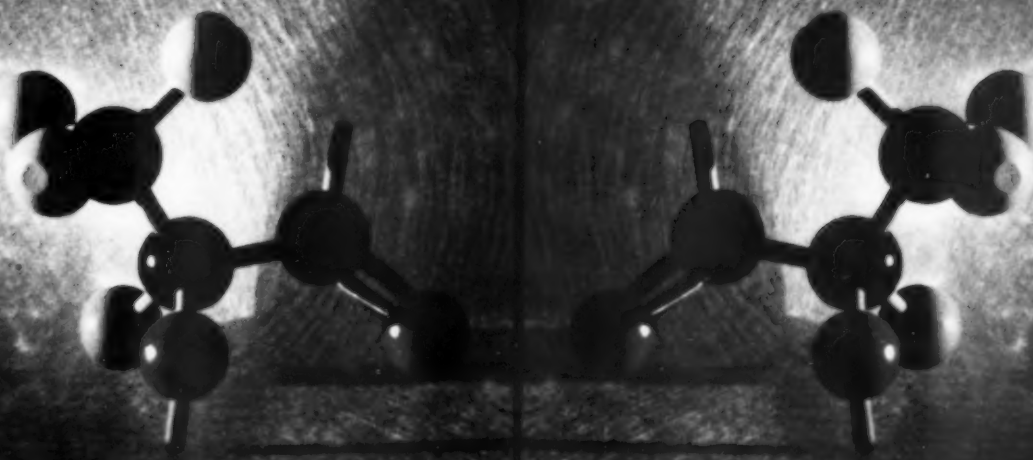

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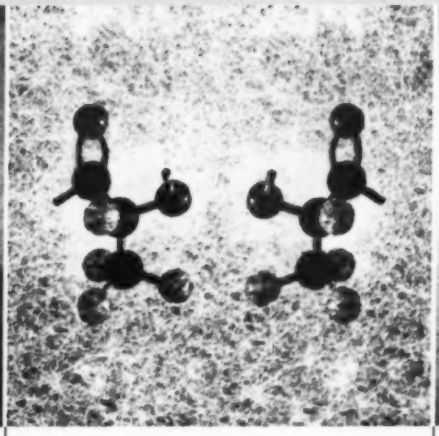
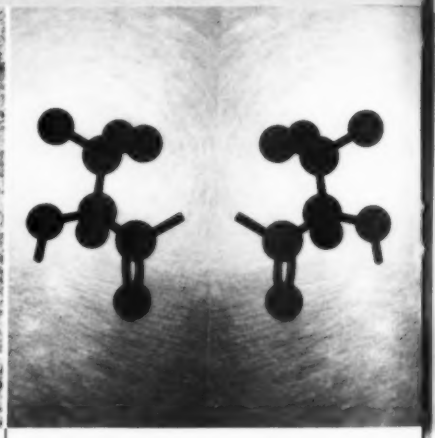


SAFER ORAL ROUTE PROVIDES HIGHER BLOOD LEVELS THAN INTRAMUSCULAR PENICILLIN G



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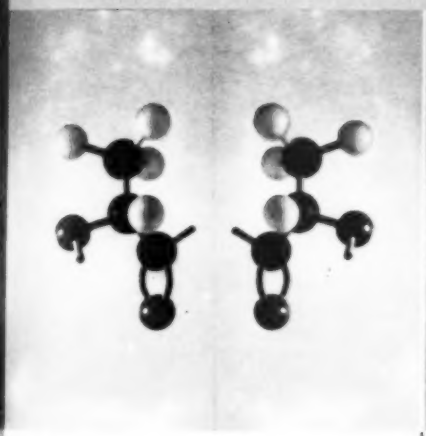
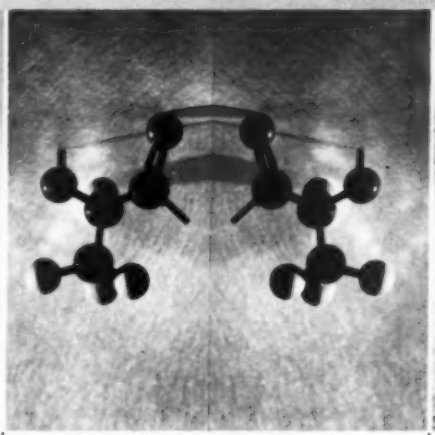
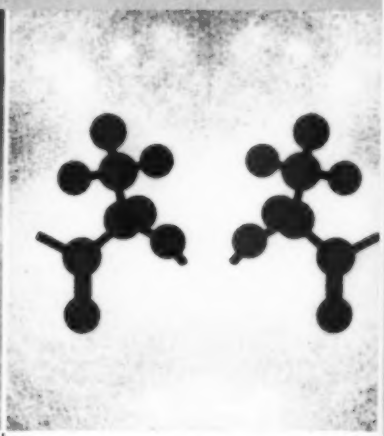






ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSE

REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE

MANY STAPH STRAINS MORE SENSITIVE TO SYNCILLIN

BRISTOL

ORIGIN OF A NEW SYNTHETIC PENICILLIN

In March, 1957, Dr. John C. Sheehan of the Massachusetts Institute of Technology announced the total synthesis of penicillin from common raw materials, thus solving a problem which had baffled research workers for more than 15 years. Although total synthesis was not commercially practicable, this work, sponsored by Bristol Laboratories, made possible the subsequent synthesis of new penicillins not occurring in nature. Later scientists at Beecham Laboratories in England discovered that a key intermediate (6-aminopenicillanic acid) could be produced by a fermentation process. With these achievements, large scale production of synthetic penicillins became feasible.

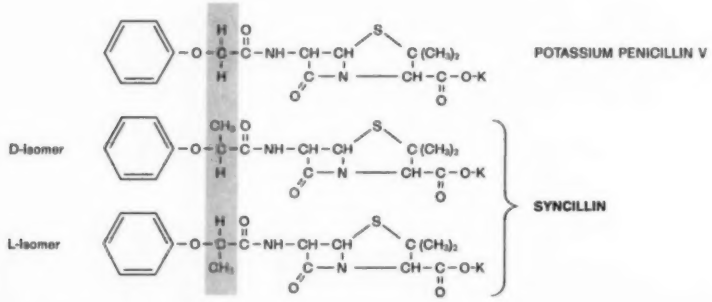
Organic chemists at Bristol then embarked upon an intensive program to develop better penicillins. Over five hundred were synthesized and underwent preliminary screening. Forty-six showed sufficient promise to warrant further investigation. Extensive microbiological, pharmacological, and clinical screening indicated that one compound, SYNCILLIN, had advantages of major importance over other penicillins.

SYNCILLIN is the N-acylation product of 6-aminopenicillanic acid and *α*-phenoxypropionic acid (the phenylether of lactic acid). It is freely soluble in water and remarkably resistant to decomposition by acid. The acid stability of SYNCILLIN is equivalent to that of penicillin V at pH 2 and pH 3 at 37° C.[1]

SIGNIFICANCE OF MOLECULAR ASYMMETRY AND ISOMERIC COMPLEMENTARITY

SYNCILLIN has a molecular configuration similar to penicillin V, but contains an additional CH_3 group so positioned as to render the adjacent carbon atom asymmetric. (In the formulae below, the added CH_3 group is shown in blue and the asymmetric carbon atom in red.) As a result, SYNCILLIN occurs as a mixture of two isomers.

Each isomer has been synthesized in essentially pure form and found to possess distinctive chemical and biological properties. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. As produced, SYNCILLIN is a mixture of the L-isomer and the D-isomer. As will be shown later, the antibiotic effect of the clinically available mixture, SYNCILLIN, is greater than either isomer alone against many organisms. This phenomenon is referred to here as *isomeric complementarity*.



SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

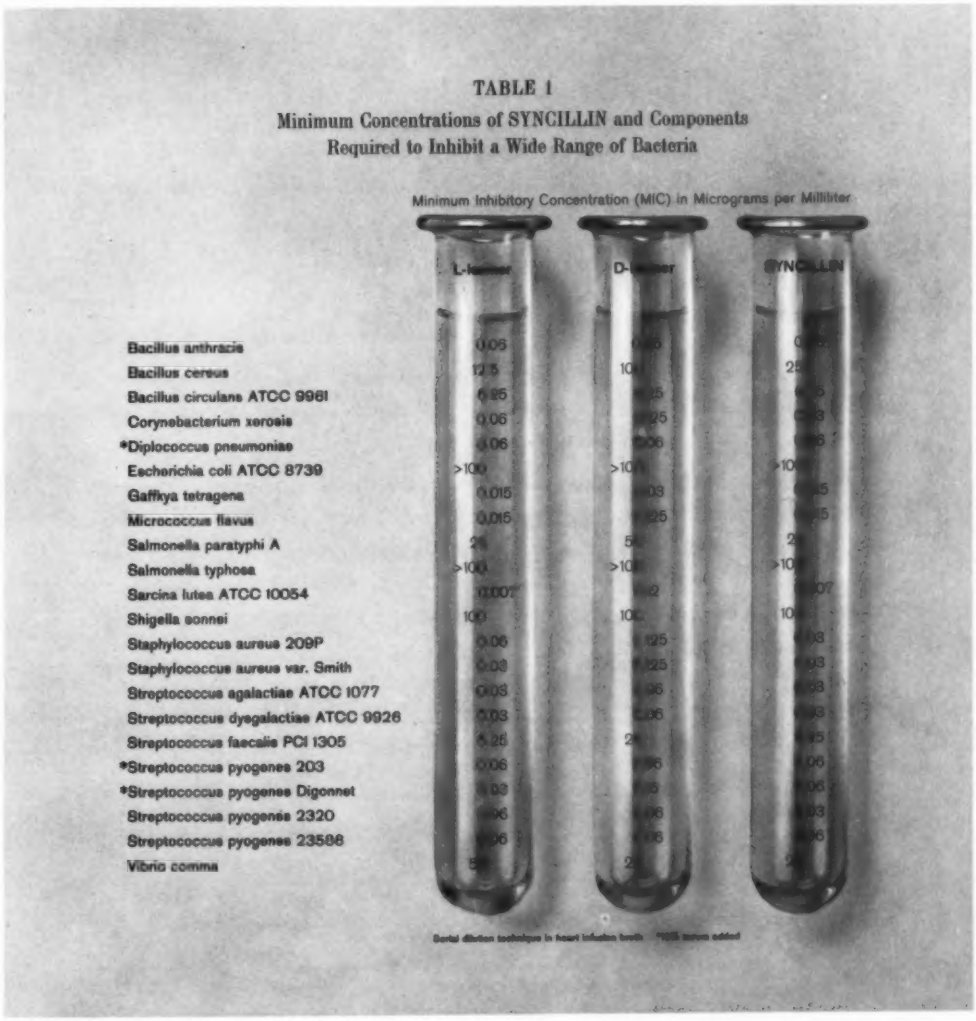
ISOMERIC COMPLEMENTARITY DEMONSTRATED IN VITRO

The *in vitro* minimum inhibitory concentration (MIC) of SYNCILLIN and of each of its two component isomers was determined for a variety of common pathogens and laboratory test organisms. As may be seen from Table 1, all three are highly effective against penicillin-susceptible staphylococci and against pneumococci, streptococci, gonococci, and corynebacteria; all are ineffective against Salmonella, *E. coli*, and other gram-negative coliform bacilli.

SYNCILLIN was more active against many of the test strains including some streptococci and staphylococci than either of its components. This demonstrates *in vitro* the phenomenon of isomeric complementarity.

TABLE 1

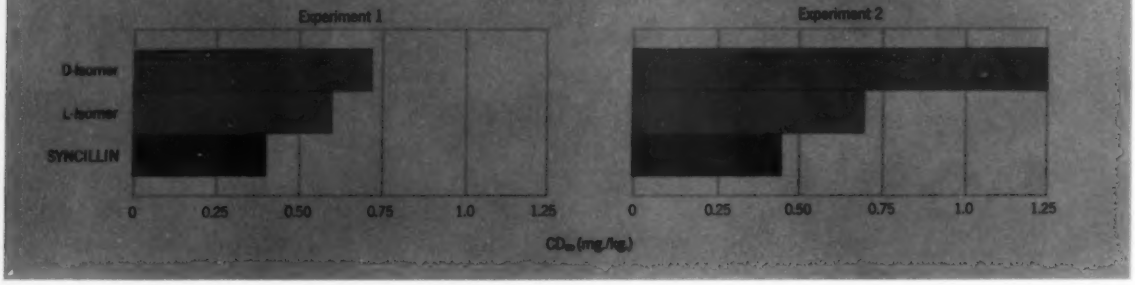
Minimum Concentrations of SYNCILLIN and Components Required to Inhibit a Wide Range of Bacteria



ISOMERIC COMPLEMENTARITY CONFIRMED IN VIVO

To determine the median curative dose (CD_{50}) mice were infected with 100 times the lethal dose of *Staphylococcus aureus*. Each penicillin being tested was administered intramuscularly at the same time, and the dose required to cure half the animals determined. The greater effect of the mixture of the two isomers (SYNCILLIN) is shown in two independent experiments. (See Figure 1.) Note that isomeric complementarity is thus confirmed *in vivo*.

FIGURE 1 — Median Curative Dose (CD_{50}) for *Staphylococcus aureus* (var. Smith) Infections

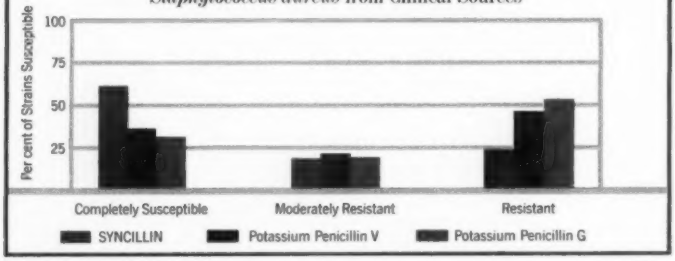


MANY STRAINS OF STAPHYLOCOCCI MORE SENSITIVE TO SYNCILLIN

SYNCILLIN has been tested against a large number of strains of *Staphylococcus aureus* isolated from clinical sources. Many organisms resistant to potassium penicillin G and potassium penicillin V proved sensitive to SYNCILLIN.

Wright[2] performed sensitivity studies on 54 strains, the majority of which were resistant or moderately resistant to penicillin V and penicillin G. Thirty-two (60%) of the strains were sensitive to SYNCILLIN, approximately twice as many as with the other penicillins. (See Figure 2.) In two-thirds of the isolates, SYNCILLIN produced inhibition at concentrations lower than those required for either of the other antibiotics. One strain was more sensitive to penicillin G.

FIGURE 2 – *In Vitro* Sensitivity of 54 Strains of Coagulase-Positive *Staphylococcus aureus* from Clinical Sources

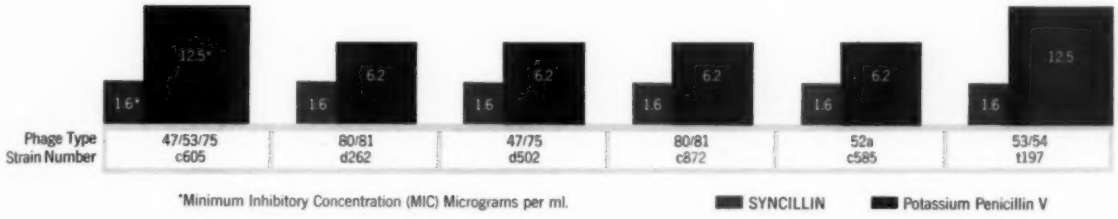


Adapted from Wright[2]

Of equal interest are the findings of White.[3] Six penicillin-resistant strains of staphylococci were isolated from hospital infections. None was sensitive to potassium penicillin V. All were sensitive to SYNCILLIN. (See Figure 3.)

FIGURE 3

Minimum Concentrations of SYNCILLIN Required to Inhibit
Hospital Strains of *Staphylococcus aureus* Resistant to Potassium Penicillin V

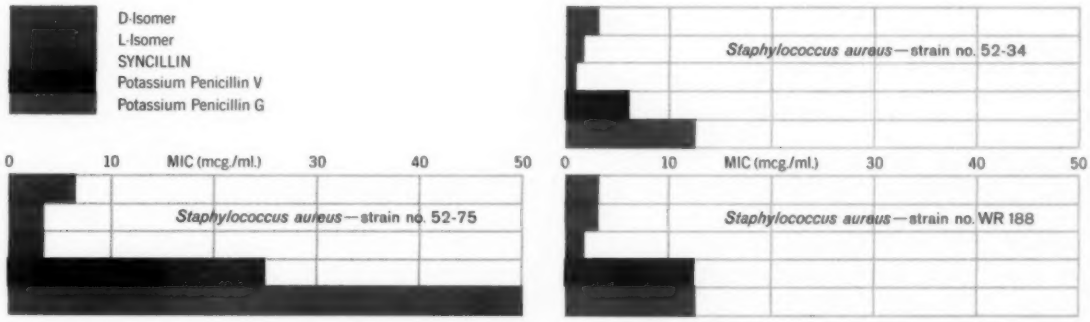


The efficacy of SYNCILLIN against the type 80/81 Staphylococcus (dangerous and widespread in hospitals) is worthy of special attention.

The complementary action of the component isomers is also seen with strains of staphylococci resistant to penicillins. Note that SYNCILLIN is more effective than either isomer against strains 52-34 and WR 188. (See Figure 4.) Against all three strains, SYNCILLIN is effective at concentrations below serum levels, while penicillins V and G are ineffective.

FIGURE 4

Minimum Inhibitory Concentrations (MIC) for Coagulase-Positive
Penicillin-Resistant Strains of *Staphylococcus aureus*



Isomeric complementarity has thus been demonstrated for:

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figure 1)*

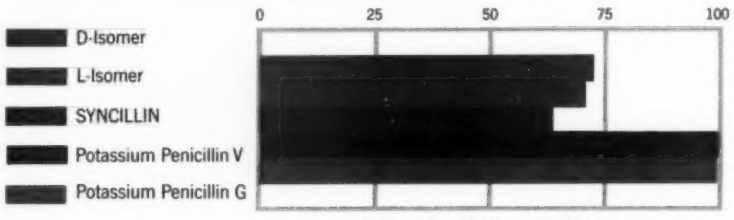
— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

ISOMERIC COMPLEMENTARITY SHOWN BY REDUCED RATE OF INACTIVATION BY PENICILLINASE

Bacterial resistance to penicillin has been attributed to the action of penicillin-inactivating enzymes produced by the invading organisms.[4] As shown in Figure 5, SYNCILLIN is less affected by staphylococcal penicillinase than either of its component isomers – a further demonstration of isomeric complementarity. Further, SYNCILLIN is shown to be less inactivated by this enzyme than penicillin V and penicillin G.

Resistance to SYNCILLIN develops in a slow, step-wise manner characteristic of other penicillins, in contrast to the usually rapid development of resistance to streptomycin.

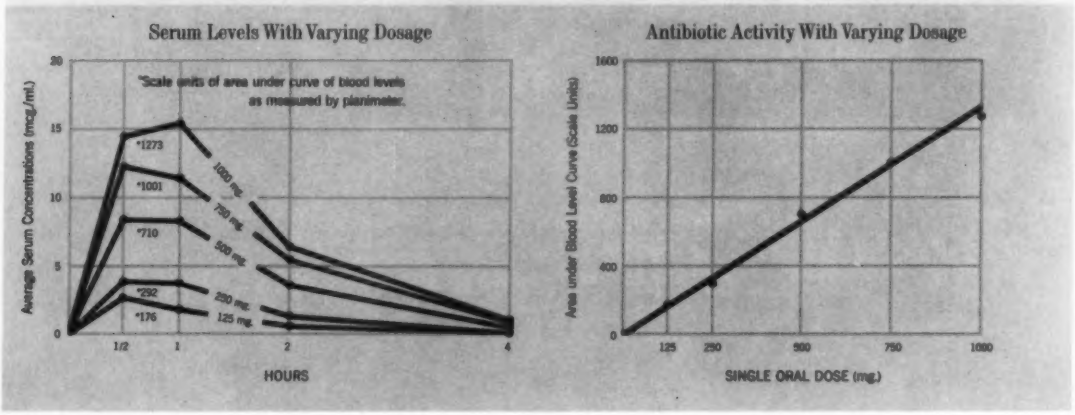
FIGURE 5—Effect of Staphylococcal Penicillinase on Different Penicillins



ANTIBIOTIC ACTIVITY DIRECTLY PROPORTIONAL TO ORAL DOSAGE

Cronk[5] studied blood levels after administering varying amounts of SYNCILLIN. (Figure 6.) Total antibiotic activity (obtained by measuring areas under curves with a planimeter) increases rapidly as the dose is doubled. These data show that increased dosage markedly increases serum concentration and thus may enhance the drug's effectiveness.

FIGURE 6



SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

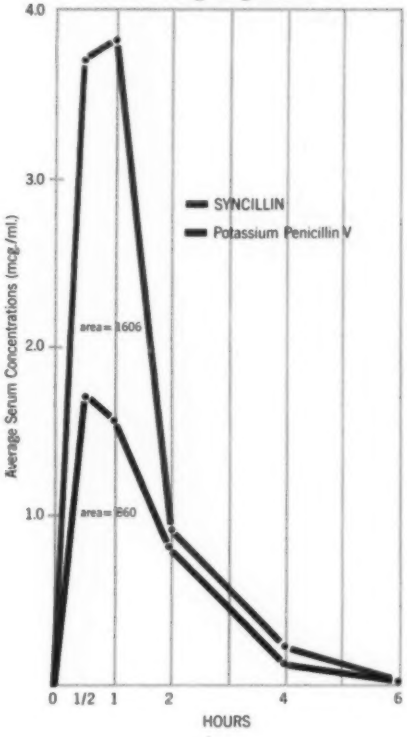
BLOOD LEVELS TWICE AS HIGH AS WITH POTASSIUM PENICILLIN V AFTER ORAL ADMINISTRATION

Wright[6] performed comparative crossover blood level studies on volunteer subjects receiving equivalent amounts of potassium penicillin V and SYNCILLIN. The peak concentrations attained during the first hour after administration were twice as high with SYNCILLIN.

The total antibiotic activity as measured by the area under the curves (see Figure 7) indicates an almost 2 to 1 superiority of SYNCILLIN (1606) over potassium penicillin V (860).

The higher blood levels may be of value with organisms of only moderate penicillin-sensitivity where doubling the blood concentration may be essential for effective bactericidal action. In addition these higher levels may be necessary where there is infection in areas with a poor blood supply.[7] Under these circumstances a higher blood concentration may provide the increased diffusion pressure required to deliver adequate amounts to the tissue.

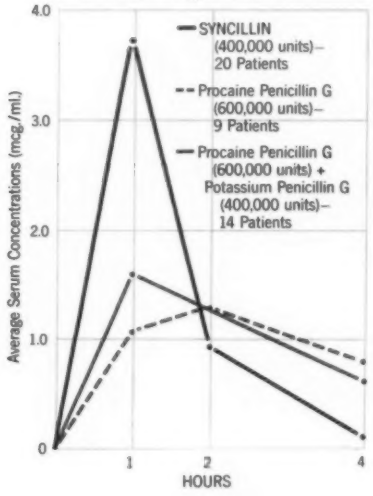
FIGURE 7
20 Subject Crossover
250 mg. Single Dose



BLOOD LEVELS MUCH HIGHER THAN WITH INTRAMUSCULAR PENICILLIN G

In addition, blood levels attained with oral SYNCILLIN[6] are much higher than those with intramuscular penicillin G.[8a, b] (See Figure 8.) Note that the level at one hour for SYNCILLIN (3.8 mcg./ml.) is more than twice as high as with procaine penicillin G, even when reinforced with potassium penicillin G (1.6 mcg./ml.). Since penicillins are *bactericidal,* these intermittent high serum levels can be clinically significant. Thus, SYNCILLIN offers the promise of superior efficacy via the safer oral route.

FIGURE 8—Serum Levels after Oral Administration of SYNCILLIN (250 mg.) and after Intramuscular Injection of Penicillin G



SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

REDUCED HAZARD OF SERIOUS ALLERGENICITY BY SAFER ORAL ROUTE

SYNCILLIN has been administered in multiple doses to 437 patients and volunteers. One patient developed itching during therapy, possibly an allergic side effect. Another had a purpuric rash, but no relationship to SYNCILLIN was established. No reactions were observed in 9 patients with a known history of sensitivity to penicillin.

While the above data suggests the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *The usual precautions for oral penicillin therapy should be observed.* Patients with histories of asthma, hay fever, urticaria, or previous penicillin-sensitivity should especially be watched carefully. Since SYNCILLIN is administered orally, it may be expected to be safer than parenteral penicillin.

As Flippin[9] recently stated, "... it is well established that serious allergy to the drug [penicillin] is most likely to occur following parenteral administration, especially after repeated intramuscular injections; the oral route is least likely to initiate severe hypersensitivity reactions. This can be explained partly by the fact that when reactions develop following oral medication, they are usually slow enough to treat symptomatically; thus the progression of the reaction can usually be interrupted. . . . In view of the relatively high incidence of severe allergy to injectable penicillin, it would seem advisable to employ oral penicillin routinely, except in the control of infections involving the blood stream, endocardium, meninges, etc., in which cases the parenteral route remains the preferred treatment."

SYNCILLIN, like other penicillins, is essentially free of other toxicity. No hematopoietic, hepatic, or renal toxicity was observed in 210 volunteers receiving 1 gm. daily for 2 to 3 weeks.[10]

CLINICAL EFFICACY DEMONSTRATED IN PENICILLIN-SENSITIVE INFECTIONS

Clinical trials conducted by Blau and Kanof,[11] White,[12] Prigot,[13] Robinson,[14] Dube,[15] Ferguson,[16] Rutenburg,[17] Richardson,[18] Bunn,[19] Cronk,[5] Kligman,[10] and Yow [20] demonstrated the efficacy of SYNCILLIN in a variety of streptococcal, staphylococcal, pneumococcal, and gonococcal infections. Conditions treated included respiratory, skin, soft tissue, wound, and chronic urinary tract infections; acute gonorrhea; cellulitis; septicemia; otitis media; gingivitis; and Vincent's angina. In a few patients SYNCILLIN was used for rheumatic fever or gonorrheal prophylaxis.

One hundred seventy-two of one hundred ninety-six patients responded favorably to SYNCILLIN. The failures included 1 patient with pustular dermatoses, 10 elderly patients with chronic urinary tract infections, 1 patient with gonorrhea, 1 patient with a gram-negative infection, and 10 patients with staphylococcal infections. Lack of response of staphylococcal infections was attributed to the presence of resistant organisms or local suppurative foci requiring drainage.

SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

Relatively few side effects were encountered. One patient experienced moderate itching of the skin which was controlled by an antihistamine. Another reported pruritus ani which did not interfere with therapy. Diarrhea occurred in 4 instances. There was one purpuric rash, but no relationship to SYNCILLIN could be established.

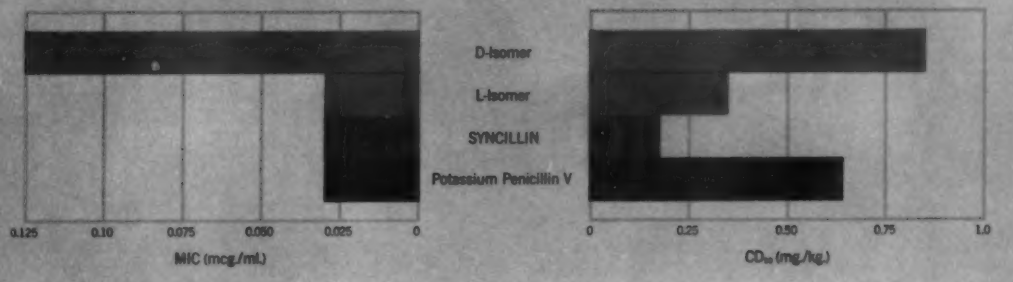
Clinical response usually begins within 24 hours in infections susceptible to SYNCILLIN. Recovery occurs in 4 to 7 days depending upon the severity of the infection. Gonorrheal infections respond very promptly to SYNCILLIN; 500 mg. b.i.d. for two days usually produce bacteriologic cures.

IMPROVED ANTIBIOTIC EFFECT FROM COMPLEMENTARY ACTION OF ISOMERS

SYNCILLIN is a mixture of isomers. The L-isomer is 2 to 17 times more active than the D-isomer against many of the organisms tested. Furthermore, the D- and L-isomers have other distinguishing chemical, pharmacological, and microbiological properties. Their *in vivo* and *in vitro* activities differ for many important pathogens. *Against many of the organisms tested, the combination of isomers* (SYNCILLIN) *is much more active than the stronger isomer alone.* This phenomenon of isomeric complementarity is not always demonstrable, for in a few instances SYNCILLIN is slightly less active.

Isomeric complementarity has previously been demonstrated *in vitro* (Figure 4) and *in vivo* (Figure 1). Figure 9 reveals a third form of superiority related to isomeric complementarity. Equal concentrations of SYNCILLIN and penicillin V were required to inhibit this growth of staphylococci *in vitro*. But, *in vivo*, a much smaller amount of SYNCILLIN *(one-third that of penicillin V)* was effective in an experimental infection with the same strain. These observations on complementary action indicated the advantage of producing the mixture of isomers as the medication to be made available for clinical therapy.

FIGURE 9 — Comparison of CD_{50} and MIC Values Against *Staphylococcus aureus* (var. Smith)



Isomeric complementarity has thus been demonstrated for:

— *certain penicillin-susceptible streptococci, staphylococci and corynebacteria* in vitro *(Table 1)*

— *penicillin-susceptible staphylococci* in vivo *(Figures 1 and 9)*

— *penicillin-resistant staphylococci* in vitro *(Figure 4)*

— *staphylococcal penicillinase antibiotic inactivation (Figure 5)*

SYNCILLIN

major therapeutic advantages accompany molecular asymmetry

Indications:

SYNCILLIN is recommended in the treatment of infections caused by pneumococci, streptococci, gonococci, corynebacteria, and penicillin-sensitive staphylococci. In addition, SYNCILLIN is effective against certain strains of staphylococci resistant to other penicillins.

SYNCILLIN, like other oral penicillins, is not recommended at the present time in deep-seated or chronic infections, subacute bacterial endocarditis, meningitis, or syphilis.

Dosage:

125 mg. or 250 mg. three times daily, depending on the severity of infection. Larger doses (e.g., 500 mg. t.i.d.) may be used for more severe infections. SYNCILLIN may be administered without regard to meals.

Beta hemolytic streptococcal infections should be treated with SYNCILLIN for at least ten days.

Precautions:

While present data suggest the possibility of reduced allergenic hazard, no definite conclusions may be drawn at this time. *Therefore the usual precautions with oral penicillin therapy must be observed.* Patients with histories of asthma, hay fever, urticaria, or previous reactions to penicillin should be watched with special care.

Diarrhea has been reported occasionally following heavy dosage. If this occurs, the interval between dosages should be lengthened.

If superinfection occurs during therapy, appropriate measures should be taken.

Since some strains of staphylococci are resistant to SYNCILLIN as well as to other penicillins, cultures and sensitivity tests should be performed where indicated by clinical judgment. As is true with all antibiotics, clinical response does not always correlate with laboratory bacterial sensitivity reports.

Supply:

125 and 250 mg. tablets, bottles of 25 and 100. 125 mg. powder for oral solution, 60 ml. vials.

References: 1. Lein, J.: Microbiology report to Bristol Laboratories Inc. 2. Wright, W. W.: Microbiology report to Bristol Laboratories Inc. 3. White, A. C.: Microbiology report to Bristol Laboratories Inc. 4. Dubos, R. J.: Bacterial and Mycotic Infections of Man, 3rd edition, Philadelphia, J. B. Lippincott Co., p. 690. 5. Cronk, G. A.: Clinical report to Bristol Laboratories Inc. 6. Wright, W. W.: Clinical report to Bristol Laboratories Inc. 7. Kass, E. H.: Am. J. Med. *18*:764 (May) 1955. 8a. White, A. C.; Couch, R. A.; Foster, F.; Calloway, J.; Hunter, W., and Knight, V.: in Welch, H. and Marti-Ibañez, F.: Antibiotics Annual — 1955-1956, Medical Encyclopedia, Inc., New York, 1956, p. 490. b. Data on file — at Bristol Laboratories. 9. Flippin, H. F.: Pennsylvania M. J. *62*:864 (June) 1959. 10. Kligman, A.: Clinical report to Bristol Laboratories Inc. 11. Blau, S., and Kanof, N.: Clinical report to Bristol Laboratories Inc. 12. White, A. C.: Clinical report to Bristol Laboratories Inc. 13. Prigot, A.: Clinical report to Bristol Laboratories Inc. 14. Robinson, C.: Clinical report to Bristol Laboratories Inc. 15. Dube, A. H.: Clinical report to Bristol Laboratories Inc. 16. Ferguson, B.: Clinical report to Bristol Laboratories Inc. 17. Rutenburg, A. M.: Clinical report to Bristol Laboratories Inc. 18. Richardson, J. H.: Clinical report to Bristol Laboratories Inc. 19. Bunn, P. A.: Clinical report to Bristol Laboratories Inc. 20. Yow, E. M.: Clinical report to Bristol Laboratories Inc.

BRISTOL

major therapeutic advantages accompany molecular asymmetry

SYNCILLIN

NIAMID*

brightens life for the aged

NIAMID gives the depressed elderly person a new sense of well-being. The family will notice a sunnier outlook, an alert interest in group activities, a renewed awareness of personal appearance, and a return of appetite. Your patient will be more cooperative and less demanding.

You can expect to see the same excellent response to NIAMID in a wide variety of depressive syndromes—acute or chronic, mild or severe, whether associated with long-standing or incurable illness, or masquerading as organic disease.

NIAMID side effects are infrequent and mild, and often lessened or eliminated by a reduction in dosage. NIAMID has not been reported to cause jaundice, and significant hypotensive effects have rarely been noted.

DOSAGE: Start with 75 mg. daily in single or divided doses, and adjust according to patient response. NIAMID acts slowly, without rapid jarring of physical or mental processes. Some patients respond to NIAMID within a few days, but for full therapeutic benefit, most require at least two weeks. NIAMID is available as 25 mg. (pink) and 100 mg. (orange) scored tablets.

Already clinically proved in several thousand patients—

Complete references and a Professional Information Booklet giving detailed information on NIAMID *are available on request from the Medical Department, Pfizer Laboratories, Division, Chas. Pfizer & Co., Inc., Brooklyn 6, N. Y.*

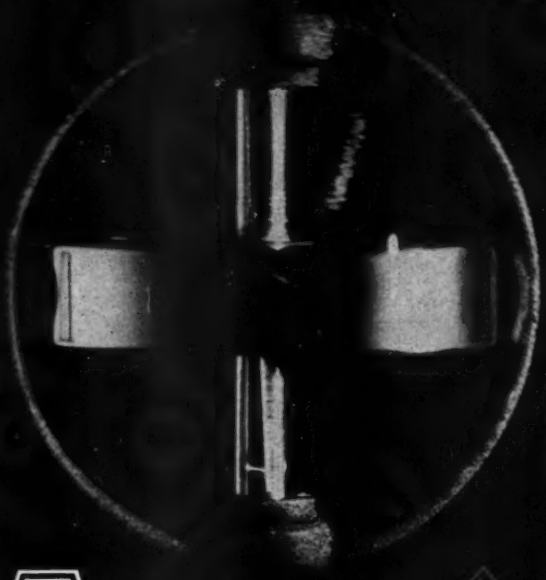
NIAMID

the mood brightener in geriatrics

*Trademark for nialamide

Pfizer *Science for the world's well-being™*

minimal disturbance
of the patient's chemical and psychic balance...



still unsurpassed for total corticosteroid benefits

Arist

Substantiated by published reports of leading clinicians:

- **effective control** of allergic and inflammatory symptoms[1-20]
- **minimal disturbance** of the patient's chemical and psychic balance[1,4,5,8-19]

stocort®

Triamcinolone LEDERLE

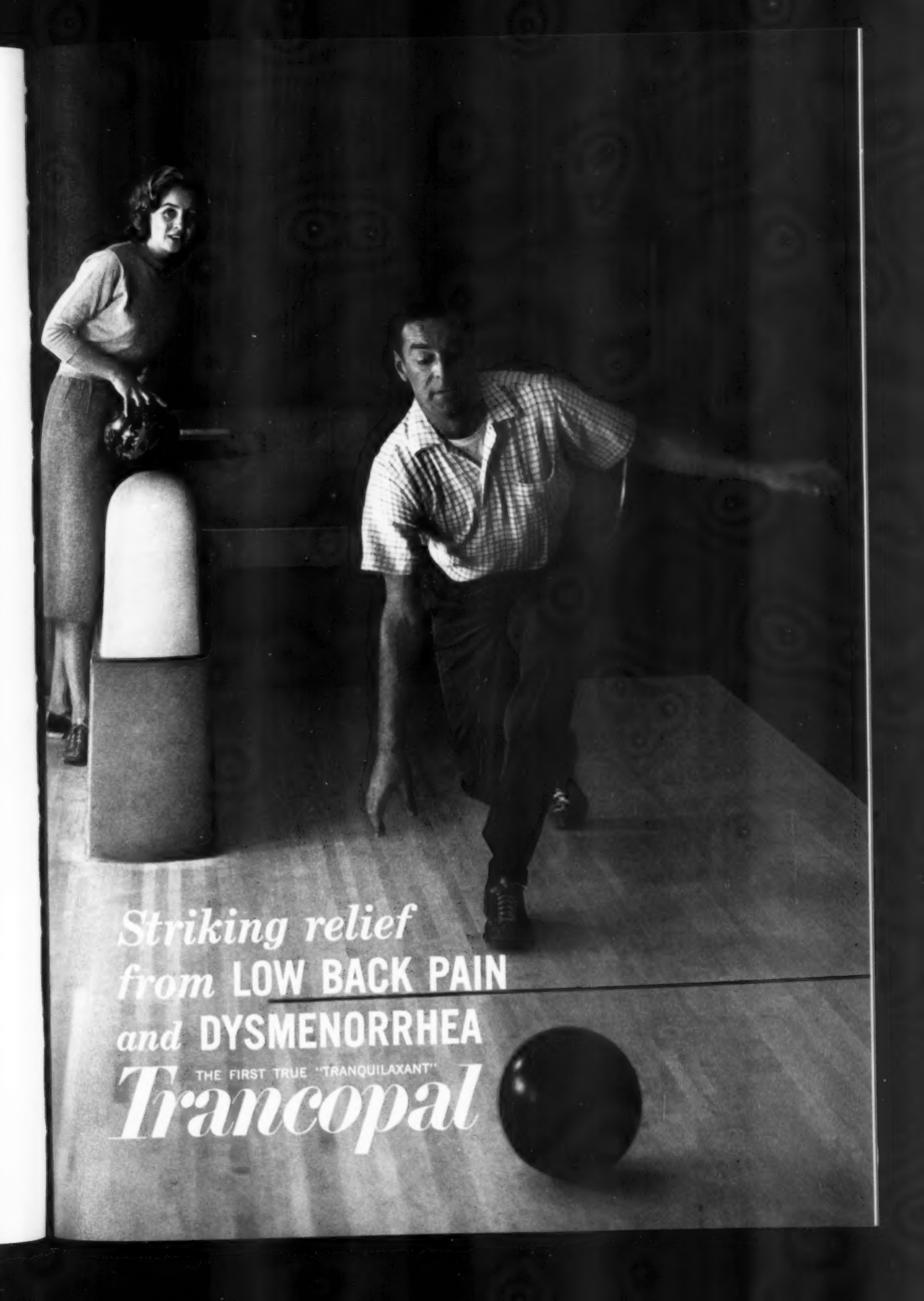
anti-inflammatory and antiallergic levels ARISTOCORT means:

- **freedom from salt and water retention**
- **virtual freedom from potassium depletion**
- **negligible calcium depletion**
- **euphoria and depression rare**
- **no voracious appetite—no excessive weight gain**
- **low incidence of peptic ulcer**
- **low incidence of osteoporosis with compression fracture**

ications: rheumatoid arthritis; arthritis; respiratory allergies; allergic and inflammatory matoses; disseminated lupus erythematosus; nephrotic syndrome; lymphomas and leukemias.
cautions: With ARISTOCORT all traditional precautions to corticosteroid therapy should be observed. Dosage should always be carefully adjusted to the smallest amount which will suppress ptoms. After patients have been on steroids for prolonged periods, discontinuance must be ried out gradually.
pplied: Scored tablets of 1 mg. (yellow); 2 mg. (pink); 4 mg. (white); 16 mg. (white).
cetate Parenteral (for intra-articular and intrasynovial injection). Vials of 5 cc. (25 mg./cc.).

References: 1. Feinberg, S.M., Feinberg, A.R., and Fisherman, E.W.: *J.A.M.A.* 167:58 (May 3) 1958. 2. Epstein, J.I. and Sherwood, H.: *Connecticut Med.* 22:822 (Dec.) 1958. 3. Friedlaender, S. and Friedlaender, A.S.: *Antibiotic Med. & Clin. Ther.* 5:315 (May) 1958. 4. Segal, M.S. and Duvenci, J.: *Bull. Tufts North East M. Center* 4:71 (April-June) 1958. 5. Segal, M.S.: Report to the A.M.A. Council on Drugs, *J.A.M.A.* 169:1063 (March 7) 1958. 6. Sherwood, H. and Cooke, R.A.: *J. Allergy* 28:97 (Mar.) 1958. 7. Duke, C.J. and Oviedo, R.: *Antibiotic Med. & Clin. Ther.* 5:710 (Dec.) 1958. 8. McGavack, T.H.: *Clin. Med.* (June) 1958. 9. Freyberg, R.H.; Berntsen, C.A., and Hellman, L.: *Arthritis and Rheumatism* 1:215 (June) 1958. 10. Hartung, E.F.: *J.A.M.A.* 167:973 (June 21) 1958. 11. Hartung, E.F.: *J. Florida Acad. Gen. Pract.* 8:18, 1958. 12. Zuckner, J.; Ramsey, R.H.; Caciolo, C., and Gantner, G.E.: *Ann. Rheum. Dis.* 17:398 (Dec.) 1958. 13. Appel, B.; Tye, M.J., and Leibsohn, E.: *Antibiotic Med. & Clin. Ther.* 5:716 (Dec.) 1958. 14. Kalz, F.: *Canad. M.A.J.* 79:400 (Sept.) 1958. 15. Mullins, J.F., and Wilson, C.J.: *Texas State J. Med.* 54:648 (Sept.) 1958. 16. Shelley, W.B.; Harun, J.S., and Pillsbury, D.M.: *J.A.M.A.* 167:959 (June 21) 1958. 17. DuBois, E.F.: *J.A.M.A.* 167:1590 (July 26) 1958. 18. McGavack, T.H.; Kao, K.T.; Leake, D.A.; Bauer, H.G., and Berger, H.E.: *Am. J. Med. Sc.* 236:720 (Dec.) 1958. 19. Council on Drugs: *J.A.M.A.* 169:257 (Jan. 17) 1959. 20. Rein, C.R.; Fleischmajer, R., and Rosenthal, A.R.: *J.A.M.A.* 165:1821 (Dec. 7) 1957.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York


Striking relief
from LOW BACK PAIN
and DYSMENORRHEA
THE FIRST TRUE "TRANQUILAXANT"
Trancopal

Here is what you can expect when you prescribe

for dysmenorrhea

and premenstrual tension

Case Profile*

A 28-year-old married woman, a secretary in a booking agency, complained of severe and consistent pain and cramps in the abdomen during her menstrual periods. Psychologically, she described the first two days as "climbing the walls." Menarche occurred at age 13. She has a regular twenty-eight day menstrual cycle and a four day menstrual period.

Trancopal was given in a dose of 100 mg. four times a day for the first two days of the four day period. In addition to the relief of the dysmenorrhea she also noticed disappearance of a "bloated feeling" that had previously annoyed her. She has now been treated with Trancopal for one and one-half years with excellent results. Other medication, such as codeine or aspirin with codeine, had relieved the pain, but the patient had had to stay home. Because her father is a physician, many commercial preparations had been tried prior to Trancopal, but no success had been achieved.

Before taking Trancopal this patient missed one day of work every month. For the past year and a half she has not missed a day because of dysmenorrhea.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal®

for low back pain

Case Profile*

A 42-year-old truck driver and mover injured his back while moving a piano. The pain radiated from the sacral region down to the region of the Achilles tendon on the right side. X-rays for ruptured disc revealed nothing pertinent. The day of the injury he was given Trancopal immediately after the physical examination. Although 100 to 200 mg. three times a day were prescribed, the patient on his own responsibility increased the dosage of Trancopal to 400 mg. three times a day. This dosage was continued for three days and then gradually reduced over a ten day period. During this time, the patient continued to drive his truck. The muscle spasm was completely controlled and no apparent side effects were noted.

For the past six months, the patient has continued to take Trancopal 100 to 200 mg. as needed for muscle spasm, particularly during strenuous days.

**Clinical Reports on file at the Department of Medical Research, Winthrop Laboratories.*

Turn page for complete listings of Indications and Dosage.

THE FIRST TRUE "TRANQUILAXANT"

Trancopal

potent MUSCLE RELAXANT

effective TRANQUILIZER

- In musculoskeletal disorders, effective in 91 per cent of patients.[1]
- In anxiety and tension states, effective in 89 per cent of patients.[1]
- Low incidence of side effects (2.3 per cent of patients). Blood pressure, pulse rate, respiration and digestive processes are unaffected by therapeutic dosage. It does not affect the hematopoietic system or liver and kidney function.
- No gastric irritation. Can be taken before meals.
- No clouding of consciousness, no euphoria or depression.

Indications [1-6]

Musculoskeletal:

Low back pain (lumbago, etc.)
Neck pain (torticollis)
Bursitis
Rheumatoid arthritis
Osteoarthritis
Disc syndrome
Fibrositis
Ankle sprain, tennis elbow
Myositis
Postoperative muscle spasm

Psychogenic:

Anxiety and tension states
Dysmenorrhea
Premenstrual tension
Asthma
Angina pectoris
Alcoholism

Now available in two strengths:

Trancopal Caplets®,
100 mg. (peach colored, scored), bottles of 100.

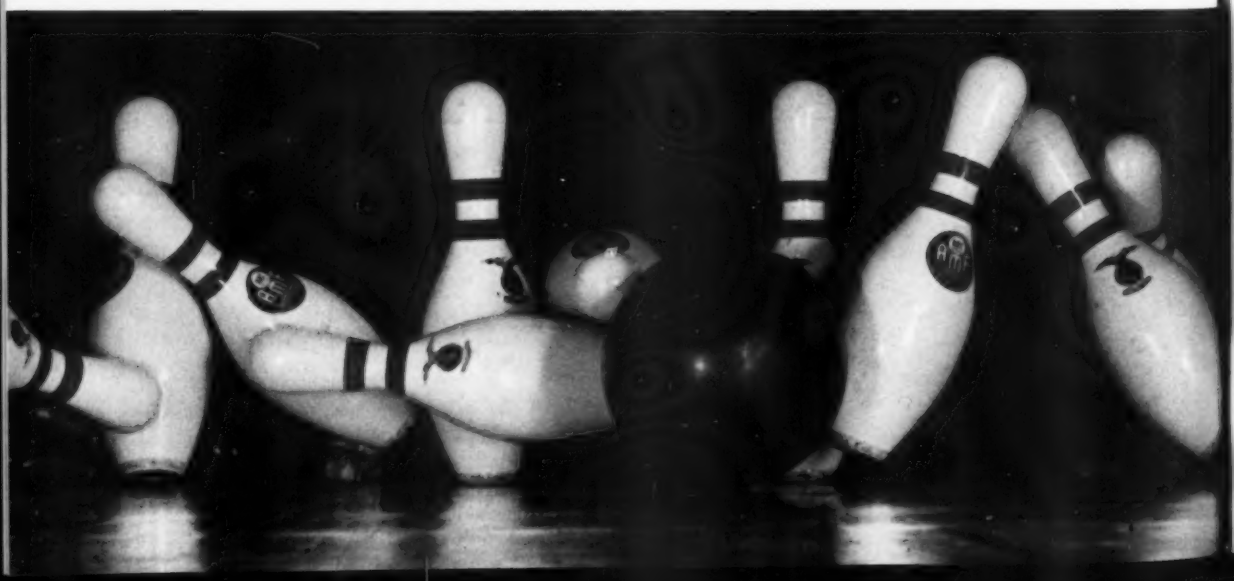
NEW STRENGTH ▶

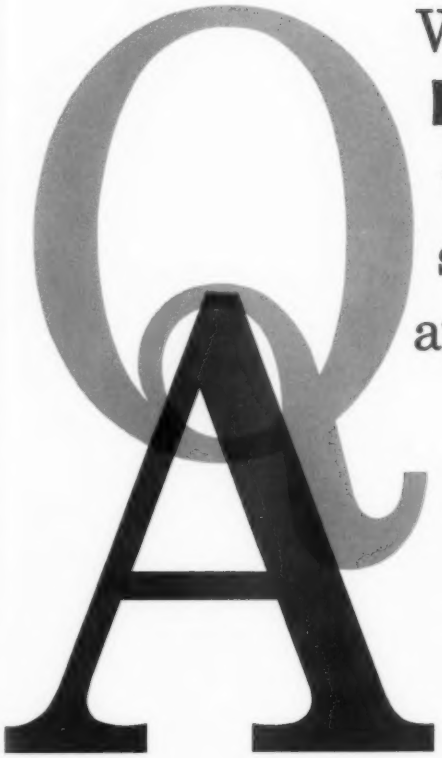
Trancopal Caplets,
200 mg. (green colored, scored), bottles of 100.

Dosage: Adults, 100 or 200 mg. orally three or four times daily. Relief of symptoms occurs in from fifteen to thirty minutes and lasts from four to six hours.

Winthrop LABORATORIES
New York 18, N. Y.

References: 1. Collective Study, Department of Medical Research, Winthrop Laboratories. 2. Lichtman, A. L.: New developments in muscle relaxant therapy, *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 3. Lichtman, A. L.: Relief of muscle spasm with a new central muscle relaxant, chlormezanone (Trancopal), Scientific Exhibit, Meeting of the International College of Surgeons, Miami Beach, Fla., Jan. 4-7, 1959. 4. Ganz, S. E.: Clinical evaluation of a new muscle relaxant (chlormethazanone), *J. Indiana M. A.* 52:1134, July, 1959. 5. Mullin, W. G., and Epifano, Leonard: Chlormezanone, a tranquilizing agent with potent skeletal muscle relaxant properties, *Am. Pract. Digest Treat.* 10:1743, Oct., 1959. 6. Shanaphy, J. F.: Chlormezanone (Trancopal) in the treatment of dysmenorrhea; a preliminary report, *Current Therap. Res.* 1:59, Oct., 1959.





Why should I use **KANTREX**® Injection* when there are so many other antibiotics available?

Because KANTREX Injection is bactericidal to a wide variety of organisms, including many that are highly resistant to the other antibiotics[3,4,10,12,13,17,18,20,21,23,24,25,27,30,33,35,37]

—organisms such as *Staph. aureus, Staph. albus, A. aerogenes, E. coli, H. pertussis, K. pneumoniae, Neisseria* sp., *Shigella, Salmonella* and many strains of *B. proteus.*

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

Next page, please . . . . . .

* Kanamycin sulfate injection (Bristol)

Q *But if I use* KANTREX *Injection, won't that help make bacteria resistant to it also?*

A A very good question, but it is reassuring to note that in almost two years of clinical use of KANTREX for the treatment of infections for which it is recommended, the emergence of KANTREX-resistant bacterial populations has not been a problem.

Q *My impression is that* KANTREX *is just another neomycin. Isn't that so?*

A Indeed not. The only thing KANTREX and neomycin have in common is a similar antimicrobial spectrum. Otherwise, they're very different: they have different chemical structures; the toxicity of KANTREX is "much less than that of neomycin"[14]; and clinically, KANTREX Injection is practical for systemic administration routinely, while neomycin is not.

Q *You mean that* KANTREX *Injection doesn't have the nephrotoxicity of neomycin?*

A Precisely. It's true that when KANTREX Injection is used, urinary casts – even slight albuminuria or microscopic hematuria – may appear, especially in poorly hydrated patients, but this does not reflect any progressive damage to the kidneys. These signs promptly disappear on adequate hydration or termination of therapy.

Q *Then why do you recommend reduced dosage in patients with renal impairment?*

A Because renal impairment causes an excessive accumulation of KANTREX in the blood and tissues, when usual doses are administered. Since KANTREX Injection is excreted entirely by the kidneys, renal impairment leads

to unnecessarily high and prolonged blood levels; and such excessive concentrations increase the risk of ototoxicity.

Q *Is that why we see reports of patients developing hearing loss during* KANTREX *Injection therapy?*

A Yes. A study of the few reported cases in which patients have suffered impaired hearing will show that in every instance they had pre-existing or concurrent renal impairment, yet received usual or excessive doses of KANTREX Injection. Dosage recommendations for KANTREX Injection emphasize that in patients with renal dysfunction, adequate serum levels can be achieved with a fraction of the dose suggested for patients with normal kidney function – with minimal risk of ototoxicity.

Q *Since urinary tract infections are often accompanied by renal impairment, does that mean I shouldn't use* KANTREX *Injection in such conditions?*

A Not at all. With proper precautions, KANTREX Injection is an excellent drug for the treatment of urinary tract infections, especially those due to *Proteus*, *A. aerogenes* and *E. coli*, even when renal impairment is present.

Q *What are the "proper precautions" in a patient with impaired renal function?*

A The package literature covers them in detail. First, the daily dose should be reduced in such a patient. Then, if he is going to receive KANTREX Injection for 7 days or more, a pre-treatment audiogram should be done, and it should be repeated at appropriate intervals during therapy. If tinnitus or subjective hearing loss develops, or if followup audiograms show significant loss of high frequency response, KANTREX therapy should be discontinued. However, therapy for 7 days or more

is seldom required because the clinical response to KANTREX Injection is so rapid.

Q *Why do you put so much emphasis on* KANTREX'S *"rapid action"? Every antibiotic I've heard about is supposed to be "rapid acting."*

A There is such an abundance of clinical evidence about "rapid acting" that it takes KANTREX Injection out of the "supposed-to" class.[1,2,3,7,8,9,11,15,16,19,21,22,26,29,32,33] Remember, the effectiveness of KANTREX Injection therapy can usually be appraised in 24 to 36 hours. That's definite evidence of rapid action. In fact, one group of investigators reported that "the rapidity with which bacteria are killed by this agent is reflected by the promptness of the clinical response."[29]

Q *Does* KANTREX *Injection cause blood dyscrasias?*

A In extensive clinical and toxicity studies by numerous investigators, as well as almost two years of general use, not a single instance of such toxicity has been reported.

Q *Can I administer* KANTREX *Injection in any other way than by the intramuscular route?*

A Yes. While it's usually given intramuscularly, other routes are practicable: intravenous, intraperitoneal, by aerosol, and as an irrigating solution. Complete instructions are included in the package insert.

Q *So you think I ought to use* KANTREX *Injection as my first choice antibiotic in staph and gram-negative infections?*

A Yes – because all evidence to date indicates that it is bactericidal against a wide range of organisms...rapid acting...does not encourage development of bacterial resistance...is well tolerated in specified dosage...and has not caused any blood dyscrasias.

KANTREX® CAPSULES

for local gastrointestinal therapy... not for systemic infections

Q *Why can't I use* KANTREX *Capsules for systemic medication?*

A Because there is only negligible absorption of KANTREX from the gastrointestinal tract.[3,5,6,8,28,34] Thus, capsules cannot provide effective blood levels.

Q *Then what are* KANTREX *Capsules used for?*

A Preoperative bowel sterilization, and local treatment of intestinal infections due to kanamycin-sensitive organisms.

Q *I've been using neomycin for preoperative bowel sterilization. Why should I switch to* KANTREX *Capsules?*

A Because KANTREX has been rated as "superior to neomycin" for this purpose.[6] It provides rapid and satisfactory control of coliforms, clostridia, staphylococci and streptococci; yeasts do not proliferate; stool concentrations of the drug are exceptionally high; and nausea, vomiting or intestinal irritation have not been observed.[5,6]

Q *What advantages do* KANTREX *Capsules offer me in the treatment of intestinal infections?*

A A high degree of effectiveness against most of the pathogens responsible for such infections: *Salmonella, Shigella, Staph. aureus, E. coli* and *Endamoeba histolytica.* Moreover, their use has been "remarkably free of any side effects."[31]

KANTREX®

INJECTION KANAMYCIN SULFATE INJECTION

INDICATIONS

Infections due to kanamycin-sensitive organisms, particularly staph or "gram-negatives": genito-urinary infections; skin, soft tissue and post-surgical infections; respiratory tract infections; septicemia and bacteremia; osteomyelitis and periostitis.

DOSAGE: INTRAMUSCULAR ROUTE

Recommended daily dose is 15 mg. per kg. of body weight, in 2 to 4 divided doses.

For intramuscular administration, KANTREX Injection should be injected deeply into the upper outer quadrant of the gluteal muscle.

TOXICITY

When the recommended precautions are followed, the incidence of toxic reactions to KANTREX is low. In well hydrated patients under 45 years of age with normal kidney function, receiving a total dose of 20 Gm. or less of KANTREX, the risk of ototoxic reactions is negligible.

In patients with renal disease and impaired renal function, the daily dose of KANTREX should be reduced in proportion to the degree of impairment to avoid accumulation of the drug in serum and tissues, thus minimizing the possibility of ototoxicity. In such patients, if therapy is expected to last 7 days or more, audiograms should be obtained prior to and during treatment. KANTREX therapy should be stopped if tinnitus or subjective hearing loss develops, or if audiograms show significant loss of high frequency response.

OTHER ROUTES OF ADMINISTRATION

KANTREX should be used by intravenous infusion only when the intramuscular route is impracticable. KANTREX can also be employed for intraperitoneal use, aerosol treatment, and as an irrigating solution. See package insert for directions.

PRECAUTIONS

Use of antibiotics may occasionally result in overgrowth of non-sensitive organisms. If superinfection appears during therapy, appropriate measures should be taken.

SUPPLY

Available in rubber-capped vials as a ready-to-use sterile aqueous solution in two concentrations (stable at room temperature indefinitely):

KANTREX Injection, 0.5 Gm. kanamycin (as sulfate) in 2 ml. volume.
KANTREX Injection, 1.0 Gm. kanamycin (as sulfate) in 3 ml. volume.

CAPSULES (for local gastrointestinal therapy; not for systemic medication)

INDICATIONS AND DOSAGE

For preoperative bowel sterilization: 1.0 Gm. (2 capsules) every hour for 4 hours, followed by 1.0 Gm. (2 capsules) every 6 hours for 36 to 72 hours.

For intestinal infections: Adults: 3.0 to 4.0 Gm. (6 to 8 capsules) per day in divided doses for 5 to 7 days. Infants and children: 50 mg. per kg. per day in 4 to 6 divided doses for 5 to 7 days.

PRECAUTION

Preoperative use of KANTREX Capsules is contraindicated in the presence of intestinal obstruction. Although only negligible amounts of KANTREX are absorbed through intact intestinal mucosa, the possibility of increased absorption from ulcerated or denuded areas should be considered.

SUPPLY

KANTREX Capsules, 0.5 Gm. kanamycin (as sulfate), bottles of 20 and 100.

REFERENCES:

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Synonyms for Pain Relief...

'TABLOID' 'EMPIRIN' COMPOUND®

Acetophenetidin ..... gr. 2½
Acetylsalicylic Acid .... gr. 3½
Caffeine ..... gr. ½

'TABLOID' 'EMPIRIN' COMPOUND® WITH CODEINE PHOSPHATE*

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*Subject to Federal Narcotic Regulations

...providing the desired gradation of potencies for relief of varying intensities of pain

IN
simple headache
rheumatic conditions
arthralgias
myalgias
common cold
toothache
earache
dysmenorrhea
neuralgia
minor trauma
tension headache
premenstrual tension
minor surgery
post-partum pain
trauma
organic disease
neoplasm
muscle spasm
colic
migraine
musculo-skeletal pains
postdental surgery
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fractures
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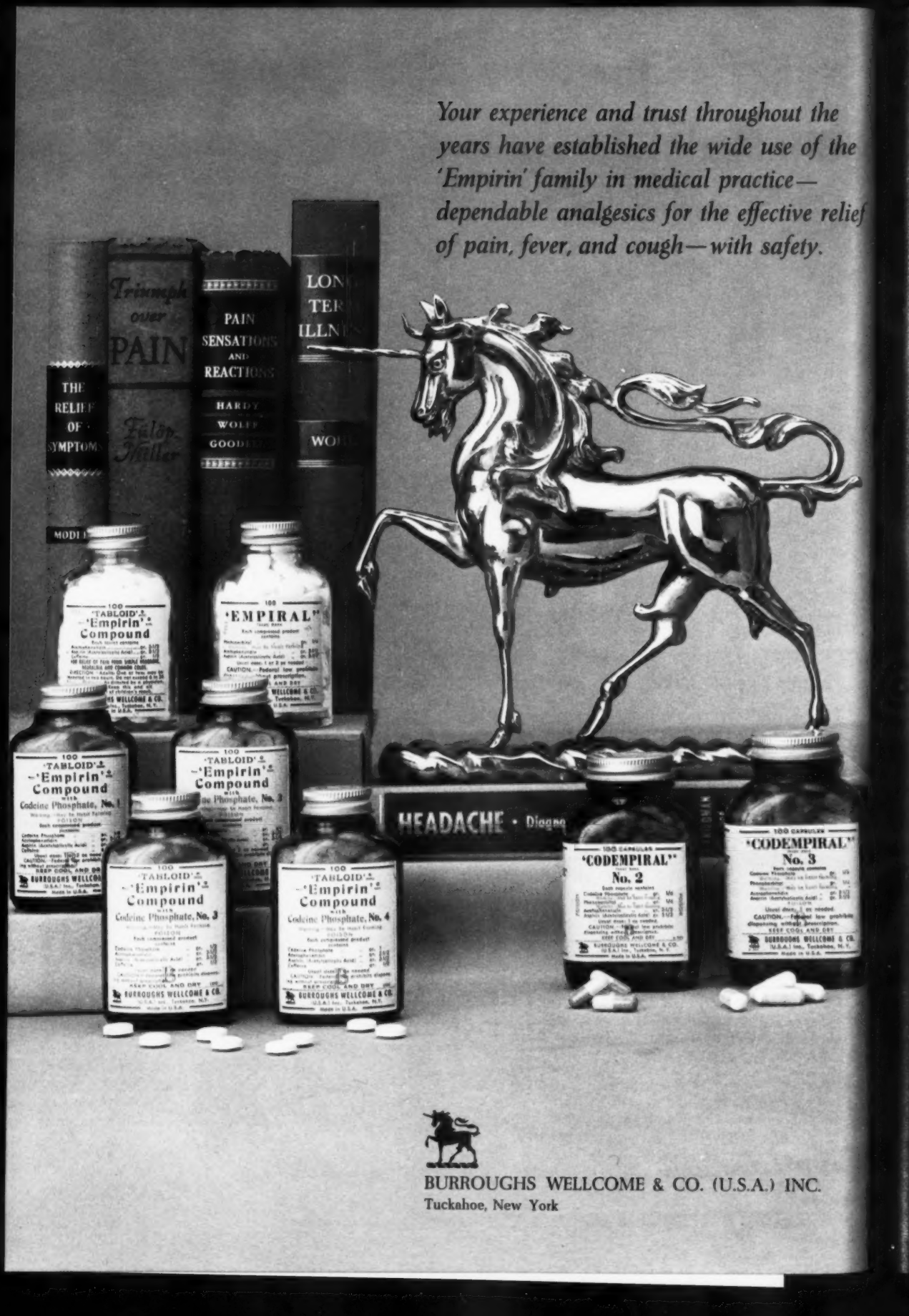
relief of pain of all degrees of severity up to that which requires morphine

AND IN
fevers
dry, unproductive coughs

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York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For the first time

CONVENIENCE and ECONOMY

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INTRAMUSCULAR SOLUTION

Initiation of therapy in *minutes after diagnosis* with new, ready-to-inject Terramycin Intramuscular Solution provides maximum, sustained absorption of potent broad-spectrum activity.

...and for continued, compatible, coordinated therapy

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oxytetracycline with glucosamine

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Continuation with oral Cosa-Terramycin every six hours will provide highly effective antibacterial serum and tissue levels for prompt infection control.

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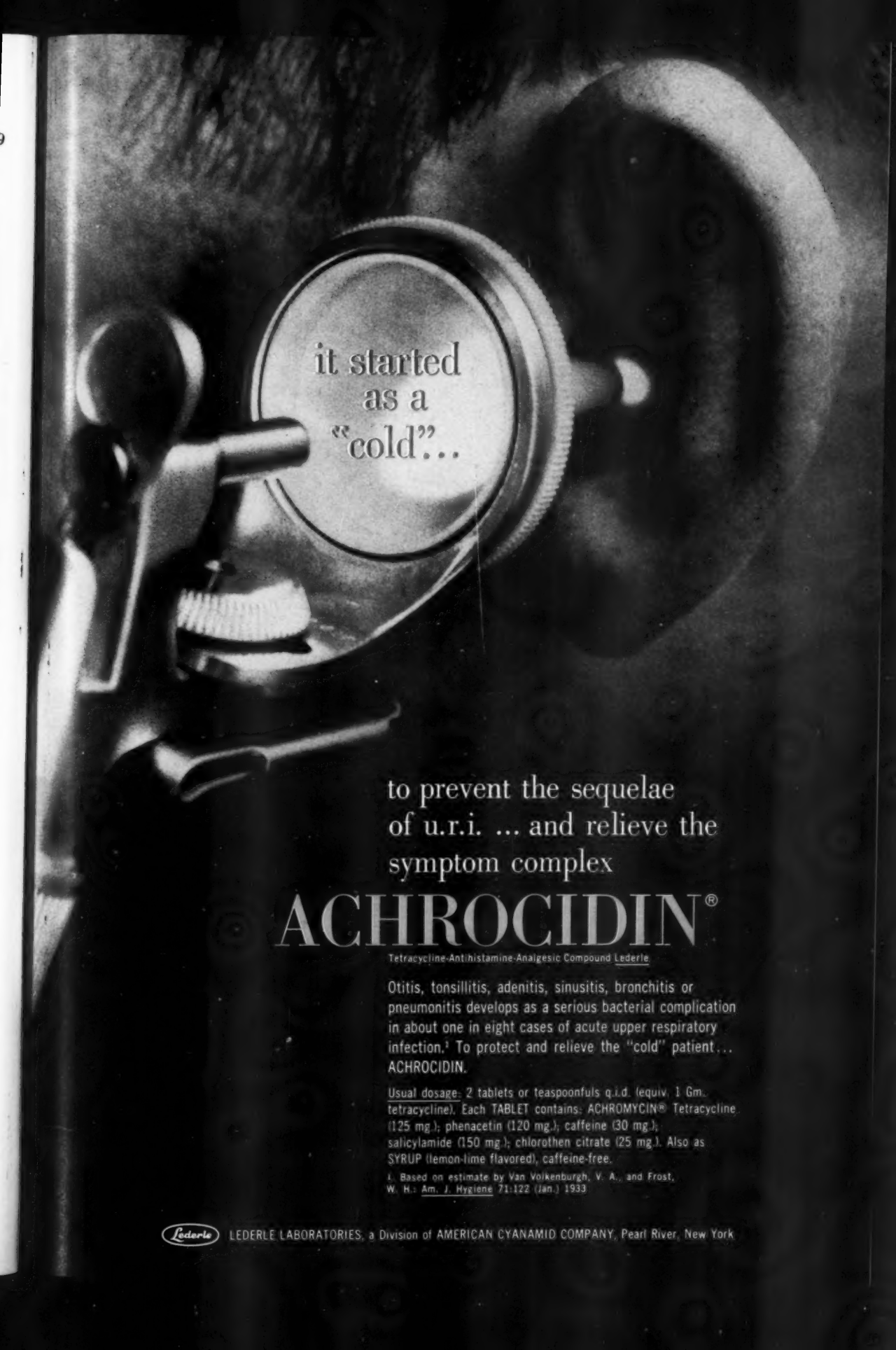

to prevent the sequelae of u.r.i. ... and relieve the symptom complex

ACHROCIDIN®

Tetracycline-Antihistamine-Analgesic Compound Lederle

Otitis, tonsillitis, adenitis, sinusitis, bronchitis or pneumonitis develops as a serious bacterial complication in about one in eight cases of acute upper respiratory infection.[1] To protect and relieve the "cold" patient... ACHROCIDIN.

Usual dosage: 2 tablets or teaspoonfuls q.i.d. (equiv. 1 Gm. tetracycline). Each TABLET contains: ACHROMYCIN® Tetracycline (125 mg.); phenacetin (120 mg.); caffeine (30 mg.); salicylamide (150 mg.); chlorothen citrate (25 mg.). Also as SYRUP (lemon-lime flavored), caffeine-free.

1. Based on estimate by Van Volkenburgh, V. A., and Frost, W. H.: Am. J. Hygiene 71:122 (Jan.) 1933

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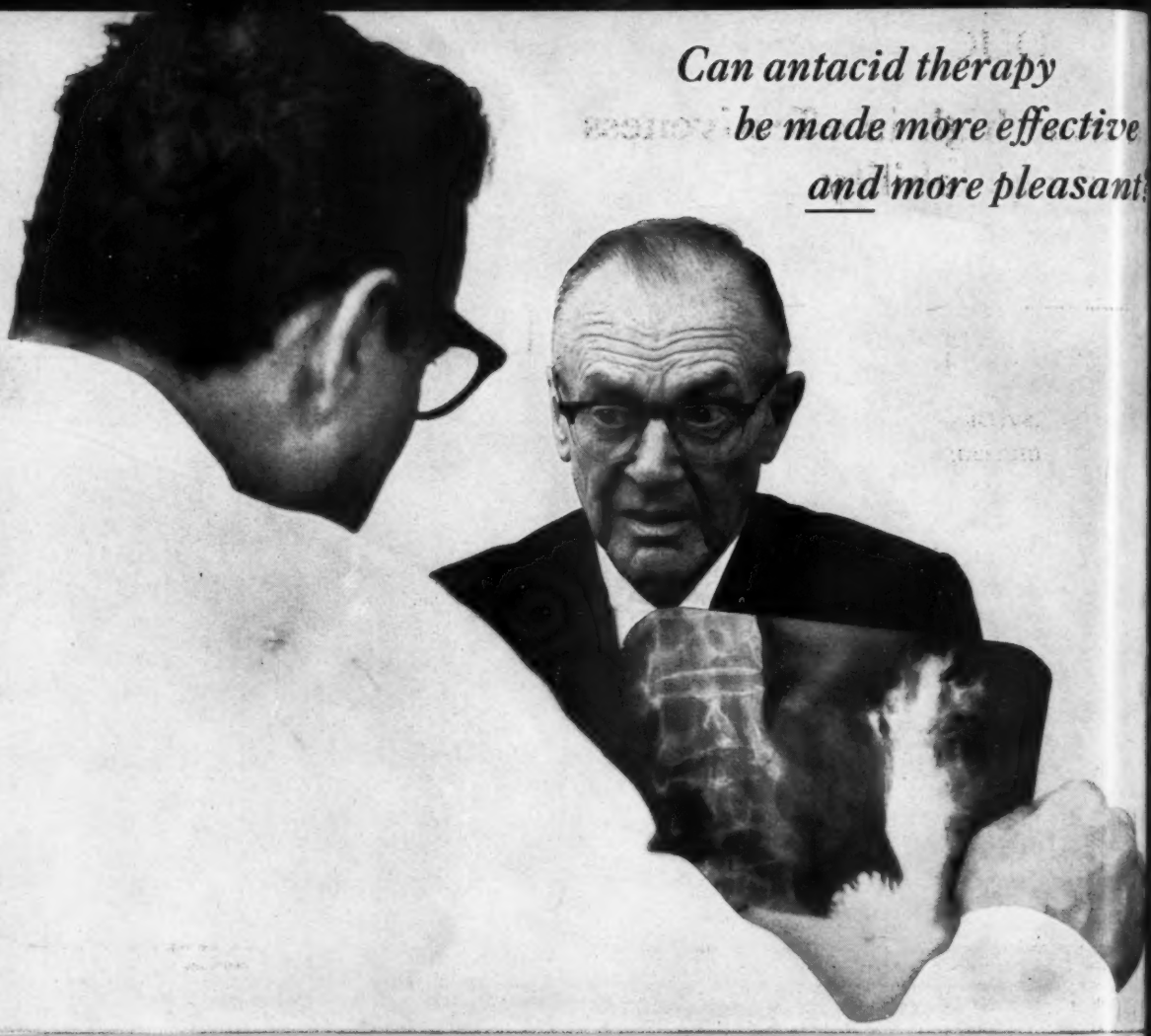

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Each Creamalin Antacid Tablet contains 320 mg. specially processed, highly reactive, short poly mer dried aluminum hydroxide gel, (stabilized with hexitol), with 75 mg. magnesium hydr oxide

1. *Neutralizes acid faster (quicker relief)*
2. *Neutralizes more acid (greater relief)*
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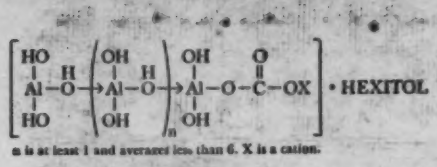
4. *No constipation · No acid rebound*
5. *More pleasant to take*

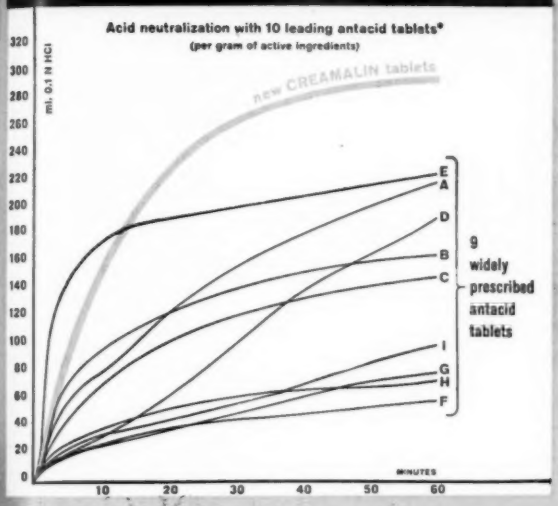
a new high in effectiveness and palatability



n is at least 1 and averages less than 6. X is a cation.

CREAMALIN NEUTRALIZES *MORE* ACID *FASTER*

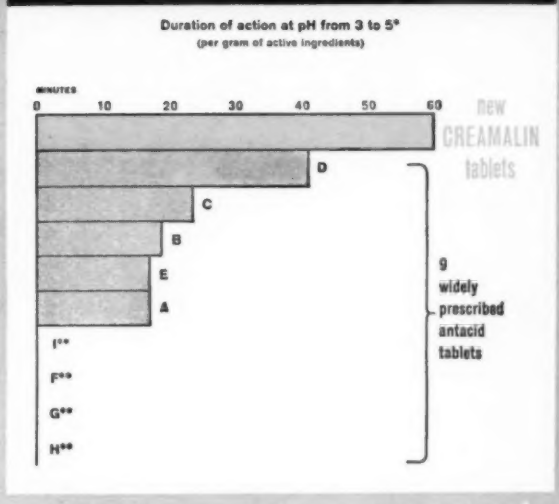
Quicker Relief • Greater Relief



Tablets were powdered and suspended in distilled water in a constant temperature container (37°C) equipped with mechanical stirrer and pH electrodes. Hydrochloric acid was added as needed to maintain pH at 3.5. Volume of acid required was recorded at frequent intervals for one hour.

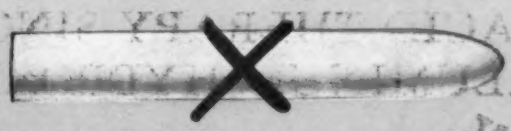
CREAMALIN NEUTRALIZES *MORE* ACID *LONGER*

More Lasting Relief



*Hinkel, E. T., Jr., Fisher, M. P. and Tainter, M. L.: A new highly reactive aluminum hydroxide complex for gastric hyperacidity. To be published.
**pH stayed below 3.

Do antacids have to taste like chalk?



No chalky taste. New CREAMALIN tablets are not chalky, gritty, rough or dry. They are highly palatable, soft, smooth, easy to chew, mint flavored.

• NO ACID REBOUND • NO CONSTIPATION
• NO SYSTEMIC EFFECT

Adult Dosage: Gastric hyperacidity: 2 to 4 tablets as necessary. Peptic ulcer or gastritis: 2 to 4 tablets every two to four hours. Tablets may be chewed, swallowed with water or milk, or allowed to dissolve in the mouth.

Supplied: Bottles of 50, 100, 200 and 1000.

Winthrop LABORATORIES, NEW YORK 18, NEW YORK

NOW... SAFER, EFFECTIVE TRANQUILIZER THERAPY

greater specificity
of tranquilizing action
—divorced from such
"diffuse" effects as
anti-emetic action
—explains why

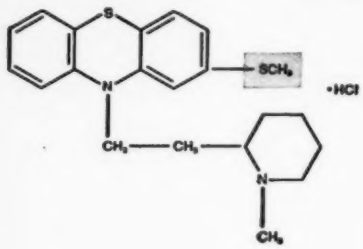
Mellaril®

THIORIDAZINE HCl

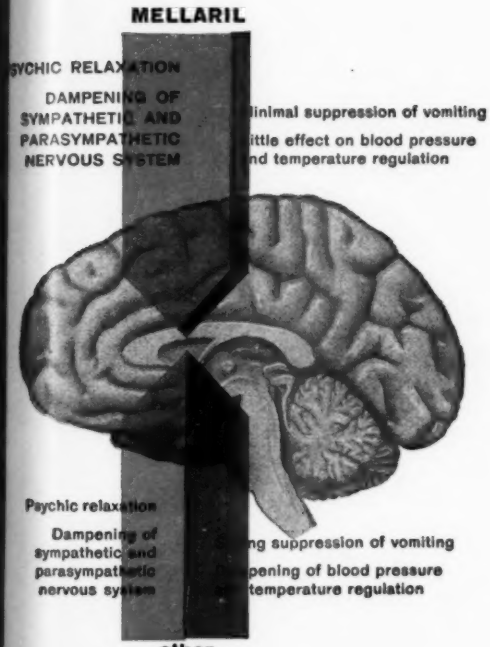
is virtually free of such toxic effects as · jaundice · Parkinsonism · blood dyscrasia

"Thioridazine [MELLARIL] is as effective as the best available phenothiazine but with appreciably less toxic effects than those demonstrated with other phenothiazines. . . . This drug appears to represent a major addition to the safe and effective treatment of a wide range of psychological disturbances seen daily in the clinics or by the general practitioner."*

new advance in tranquilization:
greater specificity of tranquilizing action results in fewer side effects



The presence of a thiomethyl radical (S-CH_3) is unique in Mellaril and could be responsible for the relative absence of side effects and greater specificity of psychotherapeutic action. This is shown clinically by:



1 **A specificity of action on certain brain sites in contrast to the more generalized or "diffuse" action of other phenothiazines. This is evidenced by a lack of appreciable anti-emetic effect.**

2 **Less "spill-over" action to other brain areas — hence, absence of undue sedation, drowsiness or autonomic nervous system disturbances.**

3 **A notable absence of extrapyramidal stimulation.**

4 **Lack of impairment of patient's normal drive and energy.**

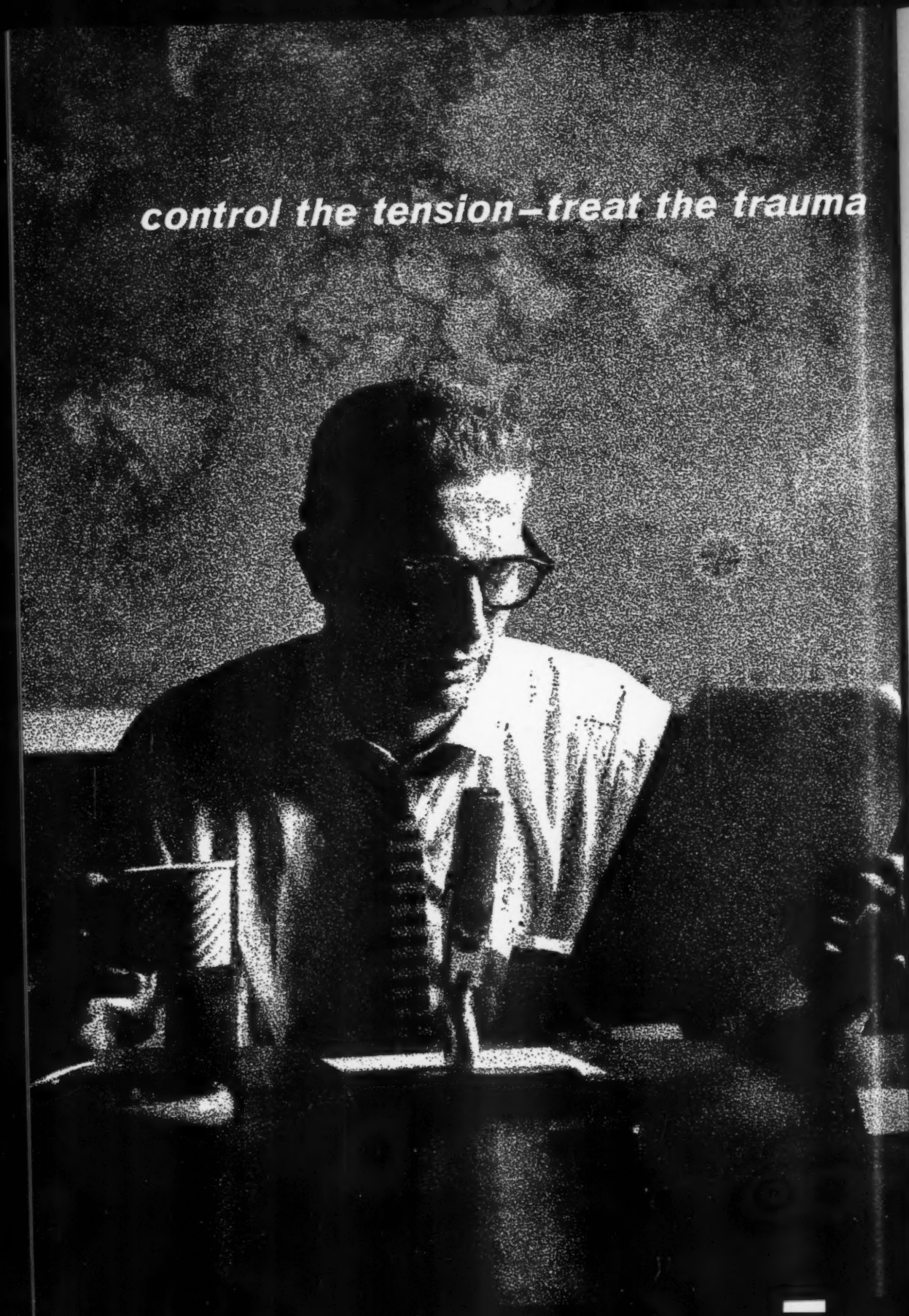
5 **Virtual freedom from such toxic effects as jaundice, photosensitivity, skin eruptions, blood forming disorders.**

INDICATION	USUAL STARTING DOSE	TOTAL DAILY DOSAGE RANGE
ADULTS: Mental and Emotional Disturbances:		
MILD—where anxiety, apprehension and tension are present	10 mg. t.i.d.	20-60 mg.
MODERATE—where agitation exists in psychoneuroses, alcoholism, intractable pain, senility, etc.	25 mg. t.i.d.	50-200 mg.
SEVERE—in agitated psychotic states as schizophrenia, manic depressive, toxic psychoses, etc.:		
Ambulatory	100 mg. t.i.d.	200-400 mg.
Hospitalized	100 mg. t.i.d.	200-800 mg.
CHILDREN: BEHAVIOR PROBLEMS IN CHILDREN	10 mg. t.i.d.	20-40 mg.

MELLARIL Tablets, 10 mg., 25 mg., 100 mg.

*Ostfeld, A. M.: Scientific Exhibit, American Academy of General Practice, San Francisco, April 6-9, 1959

SANDOZ


control the tension–treat the trauma

...Pathibamate® 400 200

meprobamate with PATHILON® tridihexethyl chloride Lederle

greater flexibility in the control of tension, hypermotility and excessive secretion in gastrointestinal dysfunctions

PATHIBAMATE combines two highly effective and well-tolerated therapeutic agents:

meprobamate (400 mg. or 200 mg.) widely accepted tranquilizer and...

PATHILON (25 mg.)—anticholinergic noted for its peripheral, atropine-like action, with few side effects.

The clinical advantages of PATHIBAMATE have been confirmed by nearly two years' experience in the treatment of duodenal ulcer; gastric ulcer; intestinal colic; spastic and irritable colon; ileitis; esophageal spasm; anxiety neurosis with gastrointestinal symptoms and gastric hypermotility.

Because of individual variation in the intensity of stimuli in gastrointestinal disorders, adequate dosage for optimum control may be expected to vary as well. The dosage strengths of PATHIBAMATE-400 and PATHIBAMATE-200 facilitate individualization of treatment in respect to both the degree of tension and associated G.I. sequelae, as well as the response of different patients to the component drugs.

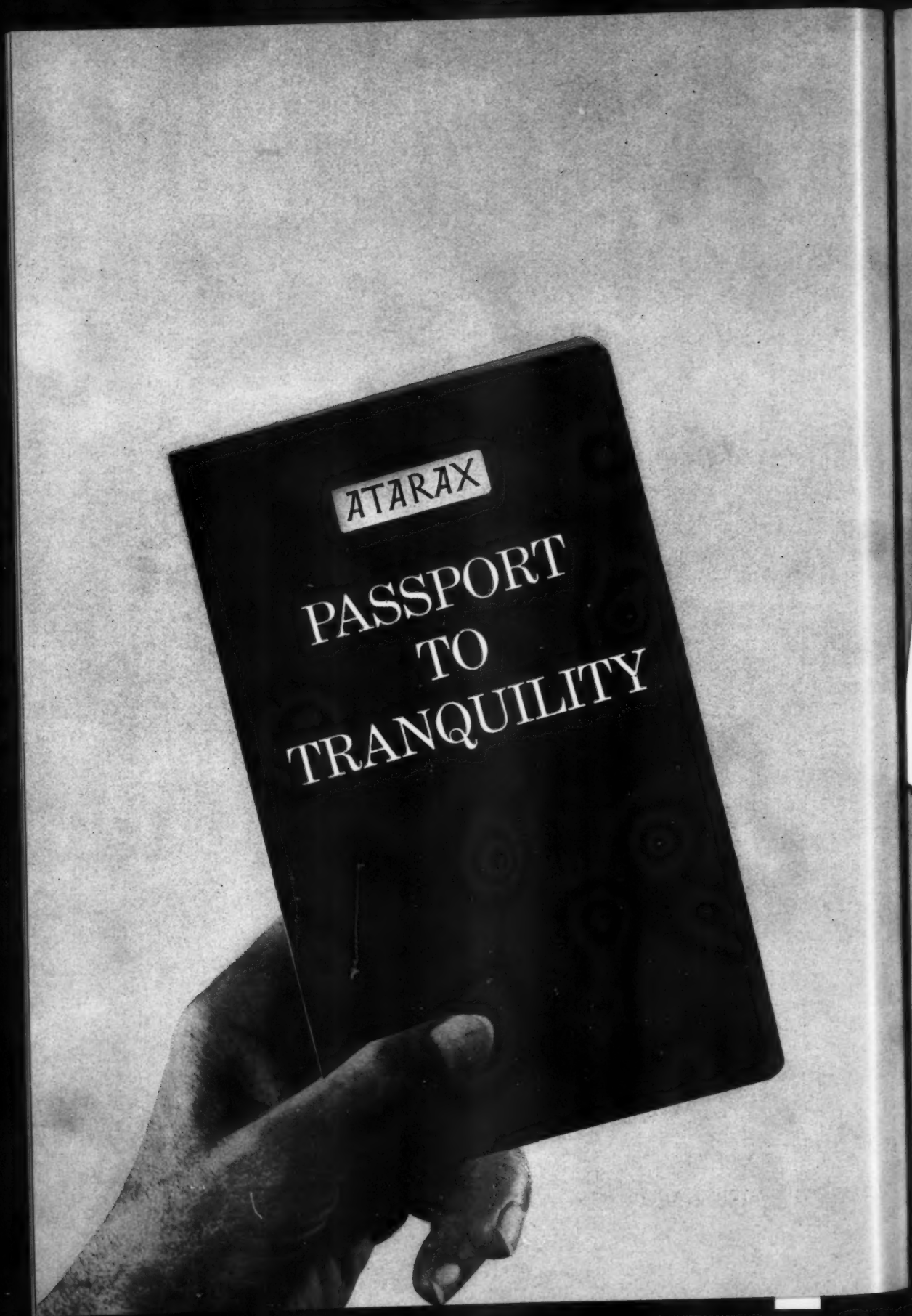
Supplied: PATHIBAMATE-400—Each tablet (yellow, 1/2-scored) contains meprobamate, 400 mg.; PATHILON tridihexethyl chloride, 25 mg.
PATHIBAMATE-200—Each tablet (yellow, coated) contains meprobamate, 200 mg.; PATHILON tridihexethyl chloride, 25 mg.

Administration and Dosage: PATHIBAMATE-400—1 tablet three times a day at mealtime and 2 tablets at bedtime.
PATHIBAMATE-200—1 or 2 tablets three times a day at mealtime and 2 tablets at bedtime.
Adjust to patient response.

Contraindications: glaucoma; pyloric obstruction, and obstruction of the urinary bladder neck.

Lederle

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York


ATARAX
PASSPORT
TO
TRANQUILITY

Passport

☞ **a universal record of effectiveness**
In anxiety, tension and agitation, ATARAX "... produced a more favorable state of calm and tranquility than any drug previously used."[1]

☞ **widest latitude of safety and flexibility**
No serious adverse reaction ever documented – five dosage forms and sizes

☞ **chemically distinct among tranquilizers**
Not a phenothiazine or a meprobamate

☞ **added frontiers of usefulness**
These unique benefits in specific indications

ANTIHISTAMINIC
ANTIARRHYTHMIC
ANTISECRETORY

BACKED BY A WORLD OF EXPERIENCE

Dosage: ADULTS, one 25 mg. tablet, or one tbsp. Syrup q.i.d. CHILDREN – 3-6 years, one 10 mg. tablet or one tsp. Syrup t.i.d.; over 6 years, two 10 mg. tablets or two tsp. Syrup t.i.d.

Supplied: Tiny 10 mg., 25 mg., and 100 mg. tablets, bottles of 100. Syrup, pint bottles. Parenteral Solution, 10 cc. multiple-dose vials.

References: 1. Farah, L.: Internat. Rec. Med. *169*:379 (June) 1956. 2. Smigel, J. O., et al.: J. Am. Geriatrics Soc. *7*:61 (Jan.) 1959. 3. Feinberg, A. R., et al.: J. Allergy *29*:358 (July) 1958. 4. Eisenberg, B. C.: J.A.M.A. *169*:14 (Jan. 3) 1959. 5. Marysael, L.: Bruxelles-méd. *38*:141 (Jan. 26) 1958. 6. Pfleger, R.: Med. Klin. *53*:1030 (June 5) 1958. 7. Over 200 laboratory and clinical papers from 14 countries.

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PASSPORT TO TRANQUILITY

(brand of hydroxyzine)

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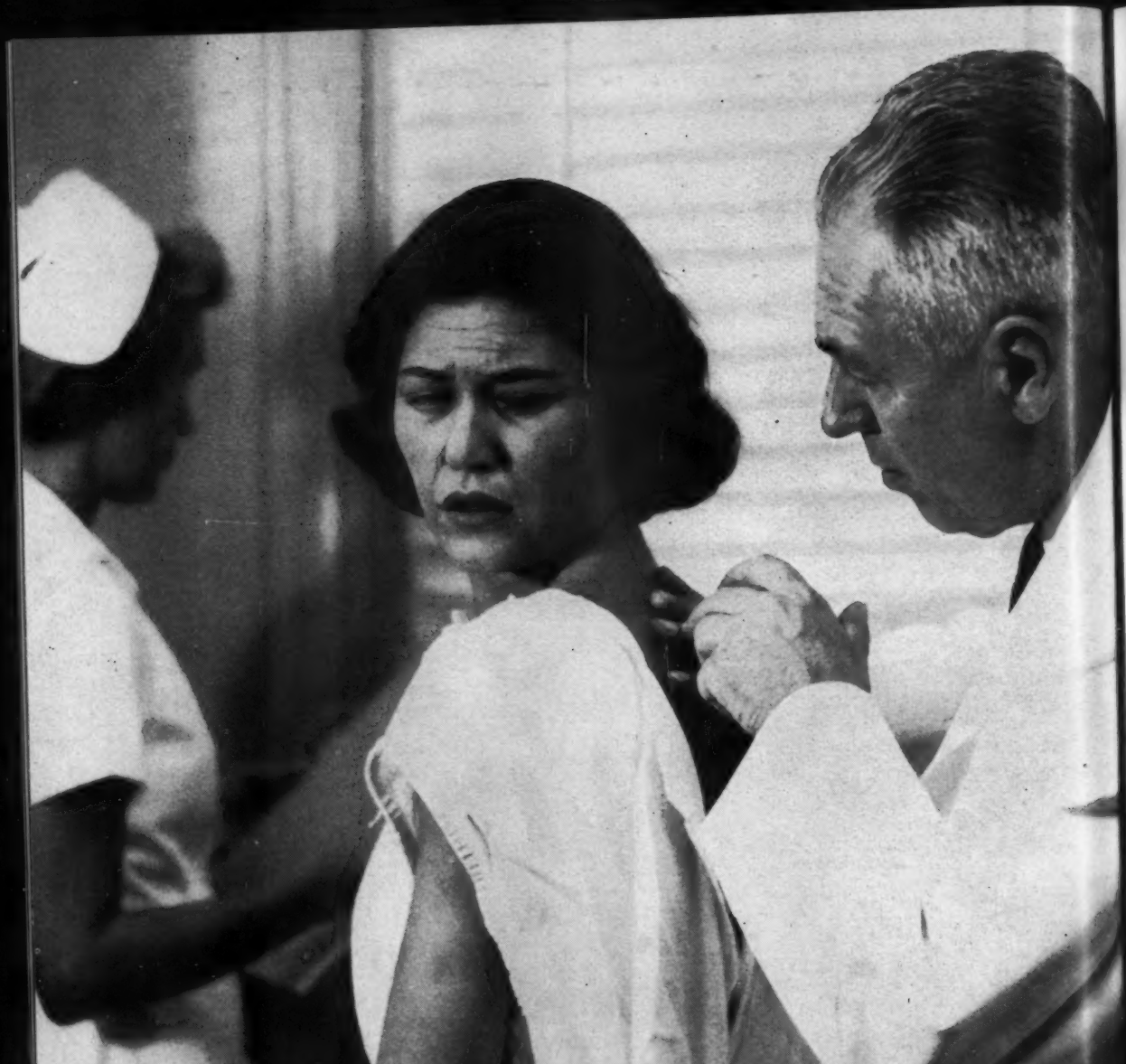

"I feel tired even after a full night's sleep."

Restores normal vitality in

emotional fatigue

Deprol relieves undue tiredness, apathy and depressed moods as it calms anxiety – without the risk of liver damage or extrapyramidal symptoms frequently reported with energizers or phenothiazines.

Emotional or nervous fatigue—undue tiredness, apathy, lethargy and listlessness—cuts sharply into the patient's usual physical and mental productivity. It is one of the most common conditions seen in every medical practice. Untreated, emotional fatigue may mushroom into a depressive episode, anxiety state, chronic fatigue or a mixture of these disorders.

Deprol acts fast to relieve emotional fatigue. It overcomes tiredness and lethargy, apathy and listlessness, thus restoring normal vitality and interest before the fatigue deepens. On Deprol, improvement is achieved without producing liver toxicity, hypotension, psychotic reactions, changes in sexual function or Parkinson-like reactions associated with energizers or phenothiazines.

BIBLIOGRAPHY (10 clinical studies, 714 patients):

1. Alexander, L. (35 patients): Chemotherapy of depression—Use of meprobamate combined with benactyzine(2-diethylaminoethyl benzilate) hydrochloride. J.A.M.A.**166**:1019, March 1, 1958. **2.** Bateman, J. C. and Carlton, H. N. (50 patients): Deprol as adjunctive therapy for patients with advanced cancer. Antibiotic Med.& Clin. Therapy. In press, 1959. **3.** Bell, J. L., Tauber, H., Santy, A. and Pulito, F. (77 patients): Treatment of depressive states in office practice. Dis. Nerv. System **20**:263, June 1959. **4.** Breitner, C. (31 patients): On mental depressions. Dis. Nerv. System **20**:142, (Section Two), May 1959. **5.** McClure, C. W., Papas, P. N., Speare, G. S., Palmer, E., Slattery, J. J., Konefal, S. H., Henken, B. S., Wood, C. A. and Ceresia, G. B. (128 patients): Treatment of depression—New technics and therapy. Am. Pract. & Digest Treat. **10**:1525, Sept. 1959. **6.** Pennington, V. M. (135 patients): Meprobamate-benactyzine (Deprol) in the treatment of chronic brain syndrome, schizophrenia and senility. J. Am. Geriatrics Soc. **7**:656, Aug. 1959. **7.** Rickels, K. and Ewing, J. H. (35 patients): Deprol in depressive conditions. Dis. Nerv. System **20**:364, (Section One), Aug. 1959. **8.** Ruchwarger, A. (87 patients): Use of Deprol (meprobamate combined with benactyzine hydrochloride) in the office treatment of depression. M. Ann. District of Columbia **28**:438, Aug. 1959. **9.** Settel, E. (52 patients): Treatment of depression in the elderly with a meprobamate-benactyzine hydrochloride combination. Antibiotic Med. & Clin. Therapy. In press, 1959. **10.** Splitter, S. R. (84 patients): The care of the anxious and the depressed. Submitted for publication, 1959.

and

11. Laughlin, H. P.: The Neuroses in Clinical Practice, Saunders, Philadelphia, 1956, pp. 448-481.

▲Deprol▲®

Dosage: Usual starting dose is 1 tablet q.i.d. When necessary, this may be gradually increased up to 3 tablets q.i.d.
Composition: 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.
Supplied: Bottles of 50 light-pink, scored tablets.

CD-4B

WALLACE LABORATORIES · *New Brunswick, N. J.*

Tetracycline-Triple Sulfa Combination (TETREX® C T/S) in the Treatment of INFECTION

It is generally agreed that it is ideal to withhold antibiotic and chemotherapeutic drugs until after sensitivity tests show which antibacterial agent will be most effective. But very often, in actual practice, the physician knows that delay in starting antibacterial treatment may be detrimental to the welfare of his patient. He must then select the therapy to meet the most serious and immediate threats to the patient.

Why Combination Therapy?

Certain infections do not respond as well to a single agent as to a combination. *Hemophilus influenzae* infections, which are frequent in children, are a particularly serious threat to infants and children up to about 3 or 4 years of age since they have not yet built up any appreciable immunity. Serious complications such as influenzal pneumonia, empyema, or meningitis may develop, especially in this age group. In fact, except for those periods when meningococcal meningitis is epidemic, *H. influenzae* is the most frequent cause of meningitis.[1] This gram-negative organism is highly susceptible both to the tetracyclines and to the sulfonamides. Even in severe infections, therapeutic failure can be virtually eliminated by giving sulfonamides plus tetracycline.[1] These two agents together constitute the treatment of choice, and give better results than either alone.[2]

Sulfonamides remain the drugs of choice for all meningococcal infections, including meningitis. They readily penetrate the blood-brain barrier and pass into the cerebrospinal fluid in good concentrations.[3] In treating overwhelming meningococcal infections, and complicating infections of the upper respiratory tract caused by other organisms, the addition of tetracycline to sulfas can be valuable.[4]

In recent years the sulfonamides have again been prescribed more and more frequently. In certain serious infections, better results can be obtained with a combination of antibiotic and sulfonamide than with either drug alone (e.g., severe pneumococcal pneumonia or pneumococcal meningitis[5]). Furthermore, mixed infections, to which young children are particularly susceptible, often respond only to combination therapy such as tetracycline with sulfonamides (TETREX C T/S).

Why Triple Sulfas?

Some sulfonamides, though therapeutically useful, frequently crystallize and cause renal damage. Sulfonamide mixtures are designed to prevent this effect. It is known that different substances can coexist in solution without interfering with each other's solubility. In such a solution each component behaves as if it alone were present. Thus, a much larger total amount of sulfonamide can exist in the urine without precipitating if a mixture is administered than if the same amount of only one compound is given.

Similarly, there is less danger of hypersensitivity with mixtures. The incidence of sensitization varies directly with the dosage and is limited to the particular sulfa given. Simultaneous use of several sulfa compounds, each in partial dosage, tends to keep each drug below its own sensitization level.[3] As with all sulfonamides, it is advisable to check for possible blood dyscrasias, rash, or renal toxicity during extended administration.

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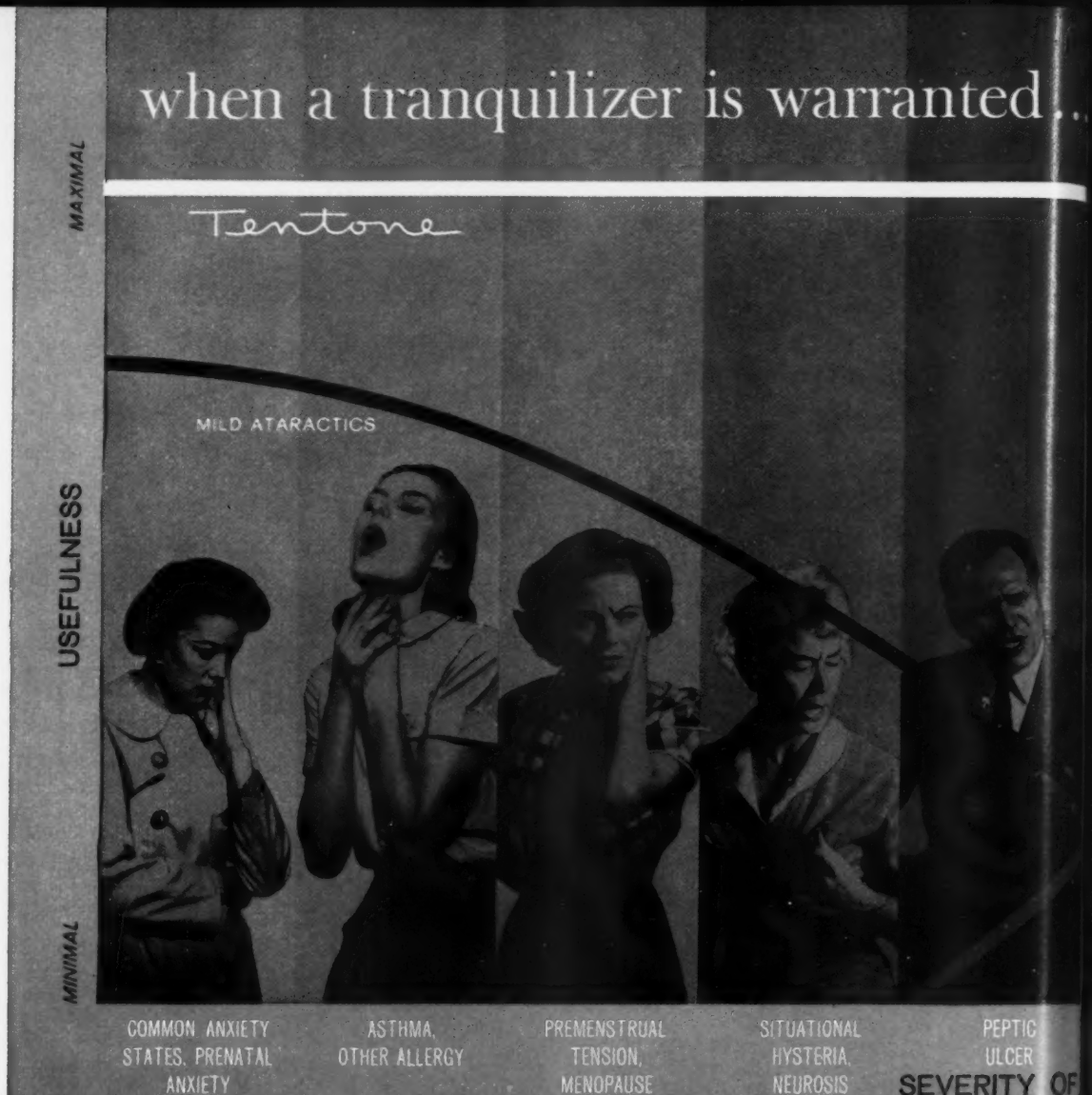

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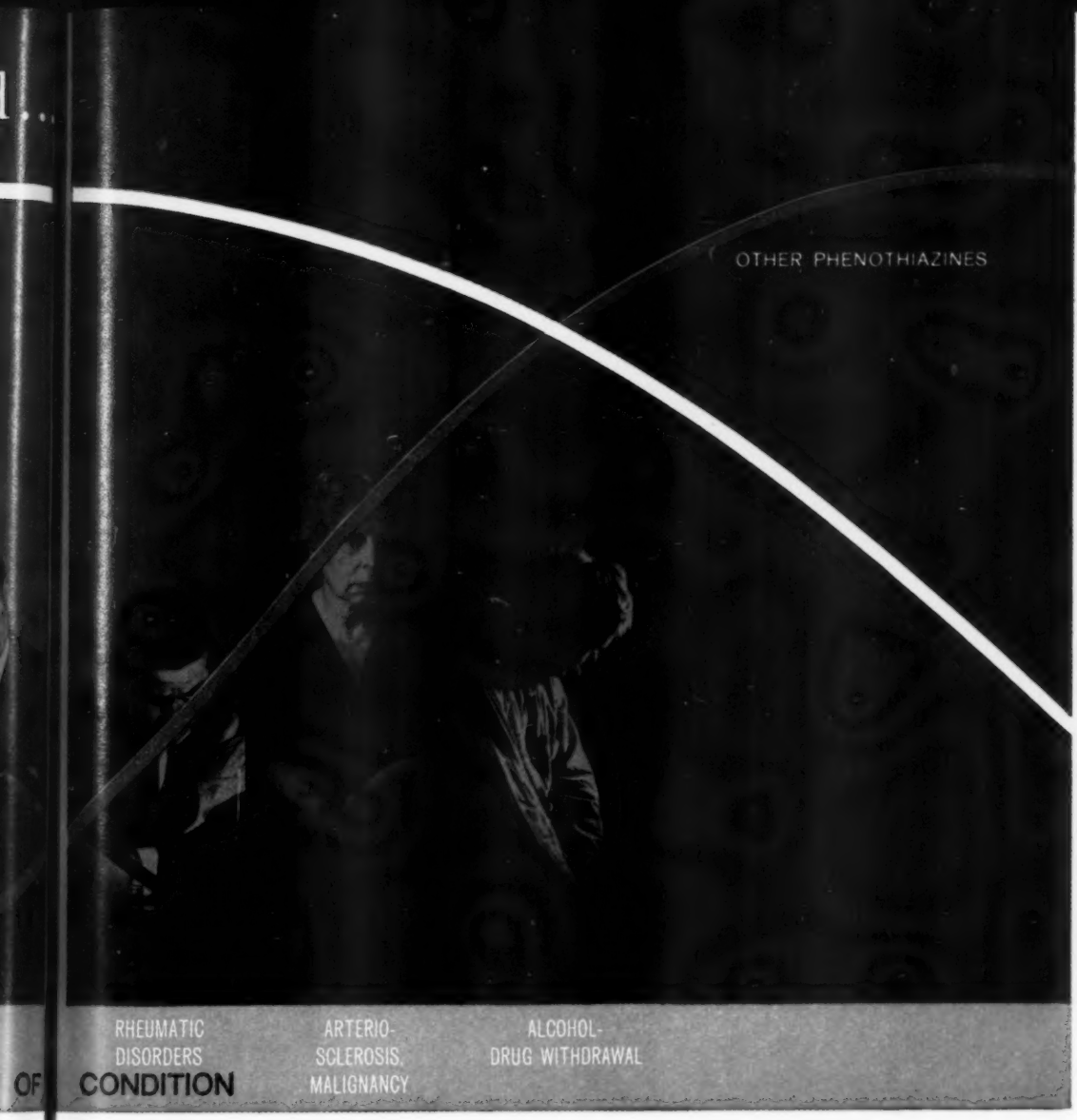

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1. Bodi, T., and Levy, H.: Clinical report, cited with permission. 2. Wetzler, R. A., and Phillips, R. M.: Clinical report, cited with permission. 3. Prigot, A.: Clinical report, cited with permission. 4. Gosline, E., *et al.*: *Am. J. Psychiat.* 115:939 (April) 1959. 5. Turvey, S. E. C.: Clinical report, cited with permission.

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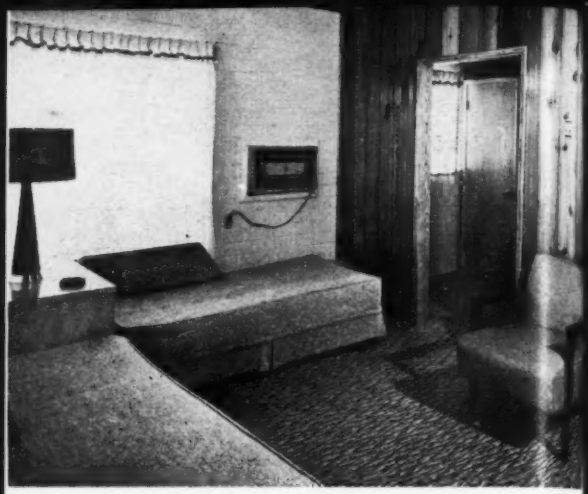

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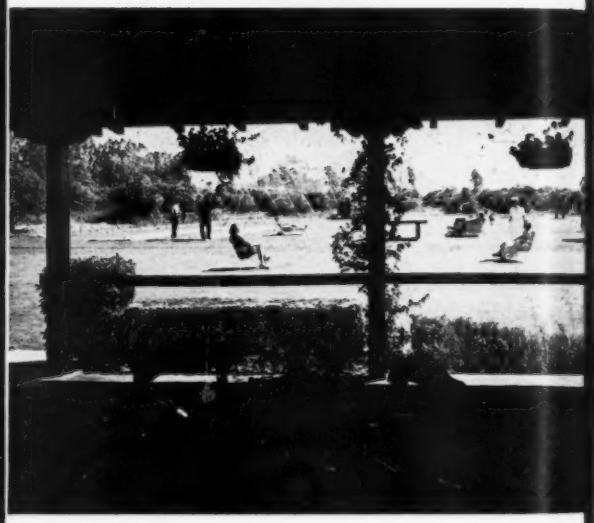

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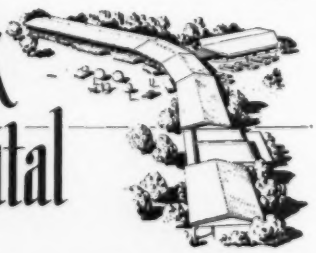

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